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Development of Pd Catalyzed Amidations & Applications to the Synthesis of Heterocycles

Adam Jason Rosenberg

Abstract

Carbon-nitrogen bond formation reaqctions are ubitquous throughout modern synthetic methods, although amide C-N bond forming reactions have only recently begun to be explored. A Pd-catalyzed amide coupling reaction was utilized in a facile synthesis of imidazo[4,5-b]pyridines and -pyrazines. This reaction provides quick access to products with substitution at N1 and C2. A model system relevant to the natural product pentosidine has been demonstrated, as well as the total synthesis of the mutagen 1-Me-5-PhIP. This reaction was then further explored to utilize more readily available catalytic components and to increase the substrate and amide scope.

The C2 amination of imidazo[4,5-*b*]pyridines was accomplished through C2 halogenation followed by substitution (S_NAr) with functionalized primary and secondary amines. This regioselective sequence is operationally simple and provides an easy access to derivatives of protected imidazo[4,5-*b*]pyridines.

Pentosidine, a biologically important advanced glycation endproduct, has been accessed in a rapid, high-yielding manner. The synthesis was accomplished via a six-step sequence starting with 3-amino-2-chloropyridine and features a palladium-catalyzed tandem cross-coupling/cyclization to construct the imidazo[4,5-b]pyridine core.

A copper catalyzed amidation of Boc protected 4-chloro-3-aminopyridine was accomplished to produce a number of aryl and heteroaryl 4-chloro-3-aminopyridines. These pyridines were used to synthesize regioselectively substituted imidazo[4,5-*c*]pyridines using a Pd-catalyzed amide coupling reaction.

A regioselective palladium-catalyzed amidation of polychlorinated aminopyridines was accomplished to provide chlorinated imidazo[4,5-*b*]pyridines. A preliminary optimization of these reaction conditions is described herein.

Development of Pd Catalyzed Amidations & Applications to the Synthesis of Heterocycles

by

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[α]	specific rotation
Å	angstrom(s)
Ac	acetyl
Anal.	combustion elemental analysis
aq	aqueous
Ar	aryl
Bn	Bzl benzyl
BOC	Boc *tert*-butoxycarbonyl
Bu	*n*-Bu normal (primary) butyl
s-Bu	*sec*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
°C	degrees Celsius
CBZ	Cbz benzyloxycarbonyl
cm	centimeter(s)
cm^{-1}	wavenumber(s)
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DMA	dimethylacetamide
DMAP	4-(*N*,*N*-dimethylamino)pyridine

DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
g	gram(s)
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	hertz
IR	infrared
J	coupling constant
k	kilo
K	kelvin(s) (absolute temperature)
L	liter(s)
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazane,
μ	micro
M	molar (moles per liter)
Me	methyl
Mes	2,4,6-trimethylphenyl (mesityl)
mM	millimolar (millimoles per liter)
mol	mole(s)
Ms	methylsulfonyl (mesyl)
MTBE	methyl *tert*-butyl ether
N	normal (equivalents per liter)
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NHC	N-heterocyclic carbine
NIS	*N*-iodosuccinimide
nm	nanometer(s)
NMP	*N*-methylpyrrolidone

NMR	nuclear magnetic resonance
Nu	nucleophile
Ph	phenyl
piv	pivaloyl
ppm	part(s) per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
*i*Pr	isopropyl
Rf	retention factor (in chromatography)
SN1	unimolecular nucleophilic substitution
SN2	bimolecular nucleophilic substitution
SN′	nucleophilic substitution with allylic rearrangement
TBAB	tetrabutylammonium bromide
TBAC	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran-2-yl
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine
TMS	trimethylsilyl; tetramethylsilane
Tr	triphenylmethyl (trityl)
Ts	*para*-toluenesulfonyl (tosyl)

PREFACE

This thesis has been adapted from the following published articles co-written by the author:

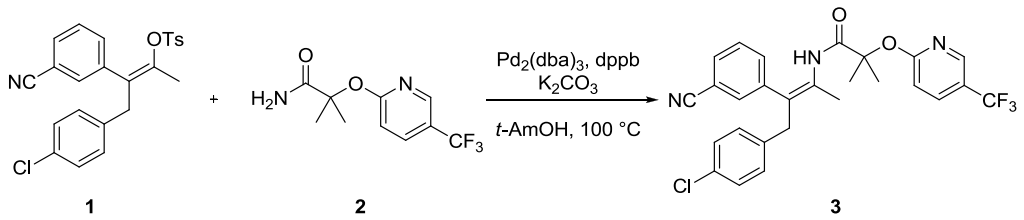
"Synthesis of Imidazo[4,5-*b*]pyridines and Imidazo[4,5-*b*]pyrazines by Palladium Catalyzed Amidation of 2-Chloro-3-amino-heterocycles" Rosenberg, A. J.; Zhao, J.; Clark, D. A. *Org. Lett.* **2012**, 14(7), 1764-1767.

"Total Synthesis of Pentosidine" Rosenberg, A. J.; Clark, D. A. *Org. Lett.* **2012**, 14(17), 4678-461.

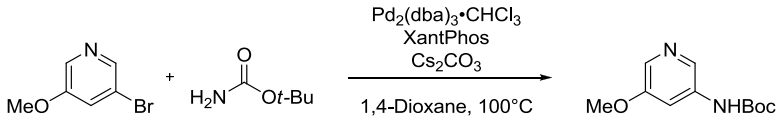
"Synthesis of 2-amino-imidazo[4,5-*b*]pyridines" Rosenberg, A. J.; Williams, T. M.; Jordan, A.; Clark, D.A. *Org. Biomol. Chem.* **2013**, 11(18), 3064-3072

1.0 INTRODUCTION

Transition-metal catalyzed bond formation has revolutionalized organic synthesis and allows straightforward access to molecules that were previously either difficult or impossible to prepare. In 2010, the Noble prize in chemistry was awarded to Heck, Negishi, and Suzuki for their pioneering work in "palladium-catalyzed cross couplings in organic synthesis."[1] However, these reactions, while extremely powerful, all focus on carbon-carbon bond formation. Carbon-nitrogen bond forming reactions have also been developed and widely used in organic synthesis almost since their inception; and have been widely reviewed.[2-6] Palladium catalyzed C-N couplings have become an increasingly important tool in heterocycle synthesis.[7-9] One facet of C-N cross-coupling reactions which have not been explored to as great a degree, is the use of more problematic coupling partners such as amides, sulfonamides, carbamates and ureas. These moieties present special challenges due to their poor nucleophilicily, potential for additional coordination to the metal catalyst, and potential deleterious side-reactions (homocoupling, reduction) under the reaction conditions. However, despite these difficulties cross-coupling conditions for these substrates have been developed and widely utilized. Some examples of palladium catalyzed amidation include the synthesis of Taranabant (**3**)[10] (Scheme 1) and the preparation of new antibiotics.[11] (Scheme 2)



Scheme 1: Pd-Catalyzed Amidation for Taranabant



Scheme 2: Pd-Catalyzed Amidation of a Carbamate

Metal catalyzed coupling reactions offer an attractive alternative to C-N bond formation due to the potential for high functional group tolerance, mild conditions, and minimization of side products.[12] In 1906, Goldberg published the first aryl amidation conditions with a copper catalyst.[13] This method required harsh conditions, with temperatures above 200°C, and provided moderate yields of the desired products. At times, stoichiometric copper was required to effect these transformations. From both a cost-efficiency and environmental standpoint, stoichiometric copper reduces the attractiveness of this method especially for industry and pharmaceutical applications. In addition, the high temperature and long reaction times limited the utility of this method. Schotten-Bauman conditions allow for the preparation of amides from acyl halides and amines in the presence of base. While this is a straightforward and useful method to prepare amides, it is limited to simple substrates that are resistant to hydrolysis.[14] Additionally, amides are often synthesized from amines and carboxylic acids, but these reactions require stoichiometric coupling reagents.[15]

As previously mentioned, amides present a special challenge when used as a coupling partner for palladium catalysis. Their poor nucleophilicity serves to create a slow ligand exchange (transmetallation step) step in the catalytic cycle, allowing for a number of other potential processes to occur. More problamatic is the potential for the formation of a κ-2 bound amide complex. (Figure 1)

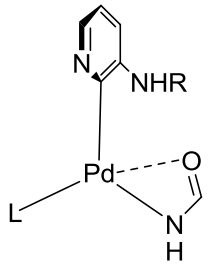
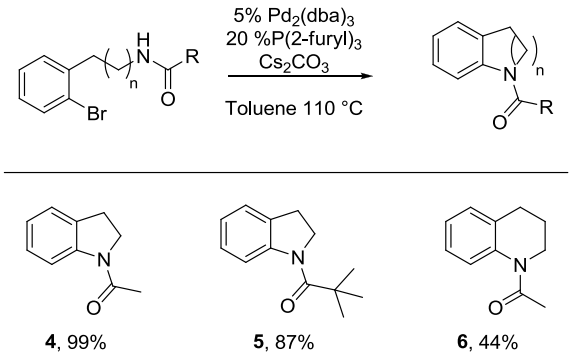


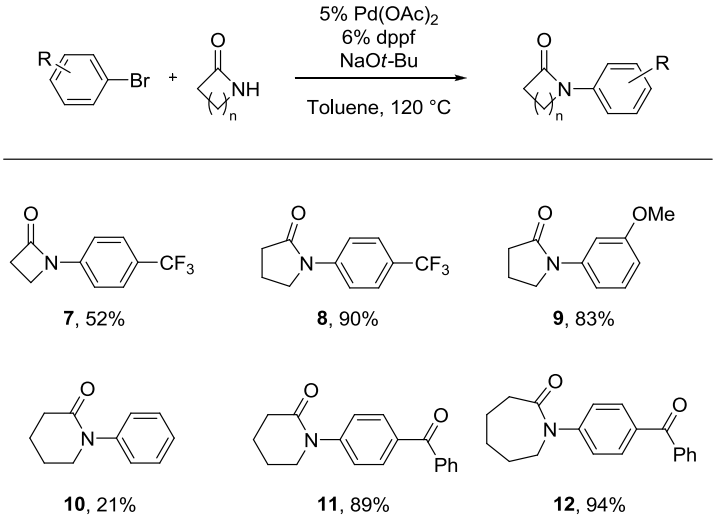
Figure 1: κ-2 Amidate

In 1996, the Buchwald group published the first successful amidation reactions using aryl halides with tethered acetamide substrates.[16] (Scheme 3). This method required high catalyst loadings and was slower than the analogous amine reactions; however, high yields could be obtained using select substrates. Optimal success was obtained when forming five-membered rings (**4, 5**); six-membered rings (**6**) could also be formed, albeit in low yield. Of note, no detectable product formation was observed when seven-membered ring formation was attempted. Efforts to apply these conditions to intermolecular coupling were unsuccessful.



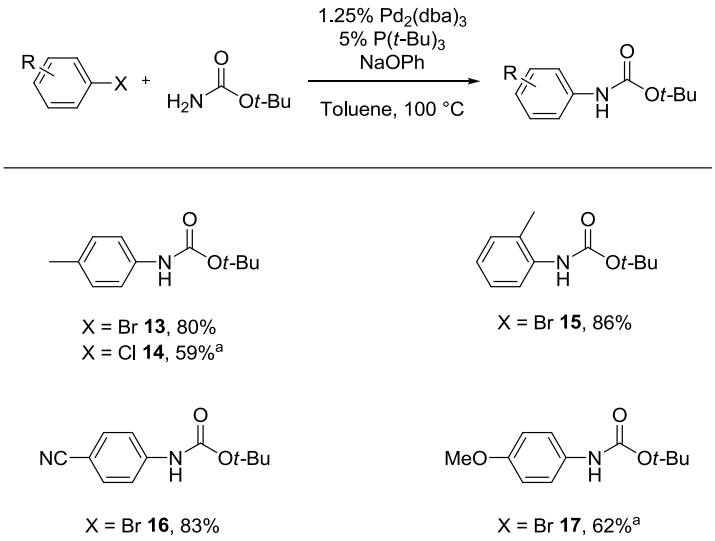
Scheme 3: Intramolecular Amidation

In 1999, Shakespeare *et al.* expanded palladium catalyzed amidation reactions to the more challenging intermolecular reaction.[17] They obtained poor to excellent yields, with variations based upon the size of the lactam employed, as well as the electronics of the aryl halide. Unfortunately, they were unsuccessful in incorporating non-cyclic amides under these reaction conditions. (Scheme 4)



Scheme 4: Shakespeare's Amide Coupling

The Hartwig group applied a similar strategy to the formation of carbamates to form Boc-protected aniline derivatives using P(*t*-Bu)$_3$ and Pd$_2$(dba)$_3$.[18] Using tri-*tert*-butylphosphine, they were able to consistently obtain good yields, while also incorporating aryl chlorides and electron-rich aryl bromides. (Scheme 5)



Scheme 5: Hartwig's Palladium Catalyzed Amidation

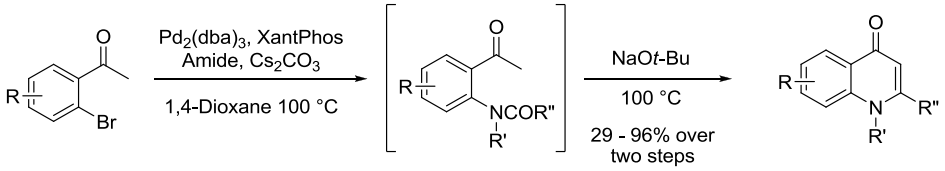
[a] 2% Pd$_2$(dba)$_3$ and 8% P(*t*-Bu)$_3$ used

The Buchwald group described the first general intermolecular amidation reactions between aryl halides and amides in 2000. Utilizing the bidentate ligand Xantphos, the reaction demonstrated high functional group tolerance and good to excellent yields.[19] Significantly, Buchwald and co-workers were able to utilize acyclic amides under these conditions.

Aryl chlorides are more attractive for cross-coupling reactions, since they are the least expensive, most readily available, and most stable aryl halide or psudeohalide coupling partners. However, they have proved to be the most challenging substrates for cross coupling chemistry.[18, 20, 21] The difference in reactivity between various halides can be advantageous for selective

coupling.[22] The Buchwald group also designed an effective ligand for the amidation of aryl chlorides based on several mechanistic observations.[23]

Palladium catalyzed amidation has also been utilized as part of a two-step one-pot reaction sequence to synthesize heterocycles through dehydration onto the resulting N-substituted amide. In 2008 Faul and co-workers reported the preparation of 4-quinolones using a palladium-catalyzed amidation on a 2'-bromoacetophenone, followed, by a subsequent Camps cyclization to give the resulting 4-quinolone.[24] (Scheme 6)

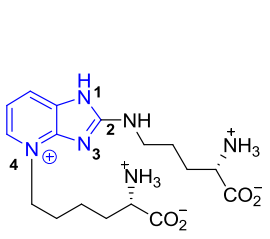


Scheme 6: Faul's Synthesis of 4-Quinolones

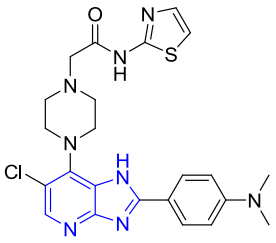
2.0 SYNTHESIS OF IMIDAZO[4,5-*B*]PYRIDINES & PYRAZINES BY PALLADIUM CATALYZED AMIDATION OF 2-CHLORO-3-AMINO-HETEROCYCLES

2.1 INTRODUCTION

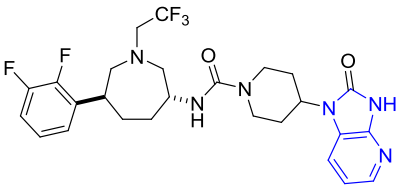
Efficient catalytic methods for the synthesis of imidazo[4,5-*b*]pyridines, especially those bearing N1 substitution, are in demand. Imidazo[4,5-*b*]pyridine derived structures are of growing interest due to their ability to function as biological mimics of the well-explored and highly developed benzimidazole core-structure.[25-27] Imidazo[4,5-*b*]pyridine derived molecules possess diverse pharmacological properties,[28] including anticancer,[29, 30] antiviral[31, 32] and other important biological activities.[33-40]



Pentosidine (18)



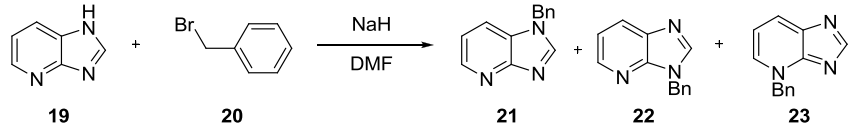
CCT129202
Aurora Kinase Inhibitor



Telcagepant (MK-0974)
CGRP Antagonist

Figure 2: Imidazopyridine Containing Structures

Despite the importance of these structures, imidazo[4,5-*b*]pyridines are difficult to prepare in a regioselective manner, especially with substitution at the N1-position. (Fig. 2) Alkylation of the unsubstituted imidazo[4,5-*b*]pyridine is remarkably unselective. For example, with sodium hydride and benzylbromide a 1:3.6:1.6 (**21**:**22**:**23**) ratio of products has been observed.[41] (Scheme 7)



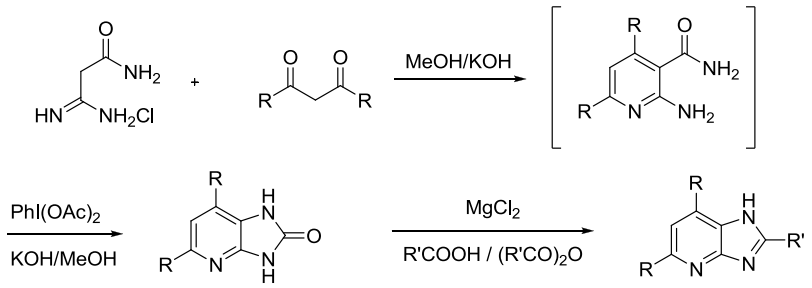
19 **20** **21** **22** **23**

Scheme 7: Alkylation of Imidazo[4,5-*b*]pyridine

The same problem exists for benzimidazole, as regioisomers are generally observed when the aryl moiety is substituted.[42] Thus, a practical and selective method for the formation of N1 substituted imidazo[4,5-*b*]pyridines was sought. A modular route that could grant access to analogues with substitution of hydrogen, carbon, halogens, and heteroatoms at C2 was highly desirable.

Many attempts have been made to address the challenges associated with the synthesis of imidazo[4,5-*b*]pyridines. In 1994 Senanayake and co-workers reported a multi-step sequence utilizing 1,3-diketones, malonamamidine salts and carboxylic acids to give 2-alkyl substituted imidazo[4,5-*b*]pyridines, however, no substitution at N1 or N3 was reported.[43] (Scheme 8) Other methods usually require the use of expensive 2,3-diaminopyridines as a starting material and/or proceed in moderate yield.[42] As such, we choose to explore a metal-catalyzed cross-coupling

route. This would allow greater product diversity and the use of the readily available and monetarily beneficial 2-chloro-3-aminopyridine.



Scheme 8: Senanayake's Approach

Recently Buchwald[44] and Ma[45] independently developed complementary syntheses of imidazo[4,5-*b*]pyridines using 2-halo-3-acylaminopyridines and amines to give N3-substituted products, with alkyl substitution at C2. However, these approaches did not allow substitution at N1 or heteroatom substitution at C2. Additionally, alkyl amines performed poorly in this reaction due to facile β-hydride elimination of the Pd(II) intermediates.[44] Buchwald and Zheng subsequently demonstrated that benzimidazole formation tolerated alkylamines with copper catalysis.[46] Ma's approach similarly utilized proline-bound copper which produced N3-substituted imidazo[4,5-*b*]pyridines.[45,47] (Figure 3)

Our interest in imidazo[4,5-*b*]pyridines originated from our work toward the total synthesis of pentosidine. (Figure 2) We desired an economical method to produce imidazo[4,5-*b*]pyridines with an electron-donating group at the N1 position[48] and an amine at the 2 position.

Our approach is conceptually distinct from those of Buchwald and Ma as we couple a protected 2-chloro-3-aminopyridine with a primary amide, followed by subsequent *in situ* cyclization and dehydration to provide the imidazo[4,5-*b*]pyridine core in a single reaction

vessel.[9, 49] (Figure 3) Protected 3-amino-2-chloropyridines are easily generated on a multigram scale by reductive amination of the chloro-aminopyridines.[50]

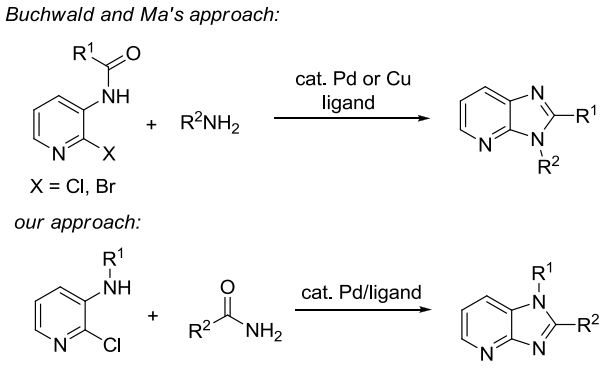


Figure 3: Imidazo[4,5-*b*]pyridine Approaches

We began our studies with known chloropyridine **24a**. This compound is highly crystalline and the product possessed the electron-withdrawing-group at N1 which we desired for the synthesis of pentosidine.

2.2 FIRST GENERATION CONDITIONS

Initial efforts to couple pyridine **24a** and formamide with standard phosphine ligands (Table 1, entries 1–5) did not show the desired reactivity, presumably due to κ^2 coordination of the formamide to the palladium center.[51,52] Next we explored ligands which have recently been shown to be effective in coupling aryl halides with amides. Both Me_4-*t*Bu-XPhos[51] (entry 8) and *t*-BuBrettPhos[53] (entry 9) gave the desired product **25a** in excellent yield and can be used interchangeably. The Bippyphos ligand[54] gave only moderate yield of **25a** (entry 7). Control experiments indicated there was no reaction in the absence of palladium; the absence of ligand also afforded no product. Additionally, no S_NAr products were obtained in the absence of both palladium and ligand. When taken together, these experiments lend evidence to a metal catalyzed cross-coupling mechanism operating under the reaction conditions (entries 10–12). Potassium phosphate base and *tert*-butanol solvent have been previously used for coupling amides and aryl halides;[51] they performed well here, granting the desired products in ≤ 4 hours in all cases under the optimized conditions. (Entries 8 & 9)

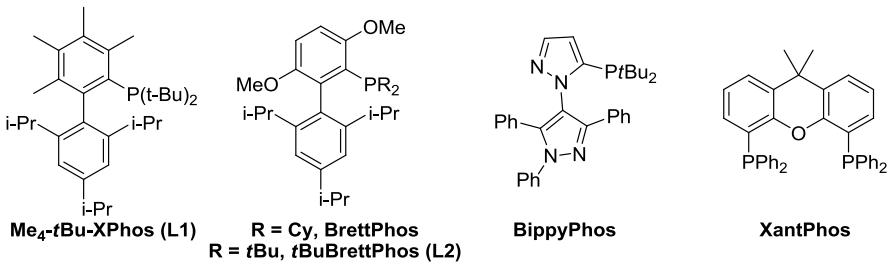
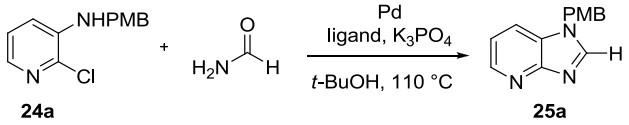


Figure 4: Ligands



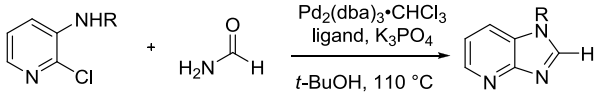
entry	Pd source	ligand	yield (%)[b]
1	$Pd_2(dba)_3{\cdot}CHCl_3$	(+/-)BINAP	NR
2	$Pd_2(dba)_3{\cdot}CHCl_3$	XantPhos	NR
3	$Pd_2(dba)_3{\cdot}CHCl_3$	$P(tBu)_3HBF_4$	NR
4	$Pd_2(dba)_3{\cdot}CHCl_3$	CatacXium A	< 5% Conv
5	$Pd_2(dba)_3{\cdot}CHCl_3$	RuPhos	NR
6	$Pd_2(dba)_3{\cdot}CHCl_3$	Brettphos	65%
7	$Pd_2(dba)_3{\cdot}CHCl_3$	BippyPhos	59%
8	$Pd_2(dba)_3{\cdot}CHCl_3$	**L1**	85-90%
9	$Pd_2(dba)_3{\cdot}CHCl_3$	**L2**	86%
10	$Pd_2(dba)_3{\cdot}CHCl_3$	-	NR
11	-	**L1**	NR
12	-	-	NR

Table 1: Reaction Optimization[a]

[a] Reaction Conditions: **24a** (0.4 mmol), Pd (0.004 mmol, 1 mol %), ligand (0.02 mmol, 5 mol %), 2 mL *t*-BuOH (0.2 M), 110 °C, 4 h. [b] Yields are of isolated products.

With optimized reaction conditions in hand, we explored the reaction scope. As shown in Table 2 the reaction produces the desired imidazo[4,5-*b*]pyridines in good to excellent yields with substituted benzyl derivatives (entries 1–4). Importantly, an aryl chloride (i.e. 2-chlorobenzyl) was tolerated under the reaction conditions (entry 5). Pyridine substitution was well tolerated at N1 despite pyridine's known ability act as a ligand on palladium (entry 6).[55, 56] Alkyl substitution was also well tolerated and no β-hydride elimination was encountered in this

reaction (entries 7–12). Excellent yields were obtained for both branched and unbranched alkyl groups. Compatibility of chiral substitution at the 1-position was also demonstrated (entries 13 & 14), and the products were isolated without racemization of either **25m** or **25n**.[57] Chiral substrates **24m** and **24n** were prepared through known Buchwald-Hartwig coupling of 3-iodo-2-chloropyridine with the desired amine.[58] Both phenyl and 4-methoxyphenyl aryl substitution were well tolerated (entries 15 & 16). Aryl substitution at N1 was installed by Chan-Lam coupling with the corresponding arylboronic acids.[59-61]



24 **25**

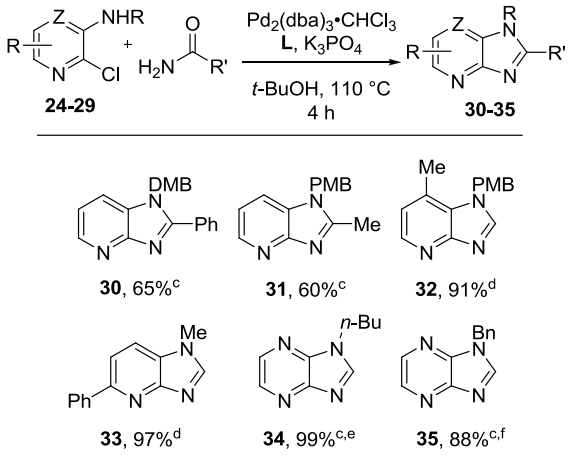
entry	R	ligand	yield (%)[b]	product
1	$CH_2(4\text{-}OMeC_6H_4)$ **24a**	**L1**	85	**25a**
2	CH_2Ph **24b**	**L1**	85	**25b**
3	$CH_2(2,4\text{-}OMeC_6H_4)$ **24c**	**L1**	82	**25c**
4	$CH_2(3\text{-}FC_6H_4)$ **24d**	**L2**	90	**25d**
5	$CH_2(2\text{-}ClC_6H_4)$ **24e**	**L2**	51	**25e**
6	CH_2(2-Pyr) **24f**	**L1**	95	**25f**
7	Cy **24g**	**L2**	90	**25g**
8	*i*-Pr **24h**	**L2**	91	**25h**
9	$CH_2C(CH_3)_3$ **24i**	**L2**	75	**25i**
10	Cyp[c] **24j**	**L2**	85	**25j**
11	$CH_2(C_6H_{11})$ **24k**	**L2**	84	**25k**
12	CH_3 **24l**	**L1**	89	**25l**
13	(*R*)-$CH(CH_3)$Ph **24m**	**L2**	77	**25m**
14	(*S*)-$CH(CH_3)$Ph **24n**	**L2**	79	**25n**
15	Ph **24o**	**L2**	90	**25o**
16	$4\text{-}OMeC_6H_4$ **24p**	**L2**	91	**25p**

Table 2: Reaction Scope[a]

[a] Reaction Conditions: **24** (0.4 mmol), Pd (0.004 mmol, 1 mol %), ligand (0.02 mmol, 5 mol %), 2 mL *t*-BuOH (0.2 M), 110 °C, 4 h. [b] Yields are of isolated products. [c] Cyp = Cyclopentyl

Although alkyl or aryl substitution at the 2 position of the imidazo[4,5-*b*]pyridine was not our primary objective, the reaction performs well when the formamide was exchanged for either

benzamide or acetamide to give the phenyl (**30**) and methyl (**31**) substituted products respectively. (Scheme 9) Other substituted amides such as cyclohexanecarboxamide coupled in 89% but failed to undergo the dehydrative cyclization, while cinnamamide gave a 3:1 mixture of uncyclized to cyclized products in 92% yield.[62] Substitution at both the 4 and 6 positions of the pyridine was well tolerated and afforded **32** and **33** in excellent yield. Pyrazines performed particularly well under the standard reaction conditions, the desired imidazo[4,5-*b*]pyrazines **34** and **25** were isolated in excellent yield with the reaction taking place up to eight-fold faster. (Scheme 9) We ascribe the rate enhancement to faster oxidative addition with the electron-deficient pyrazine moiety. Traditionally imidazo[4,5-*b*]pyrazines are prepared with a series of S_NAr reactions and cyclization with a carboxcyclic acid deriviative.[63]

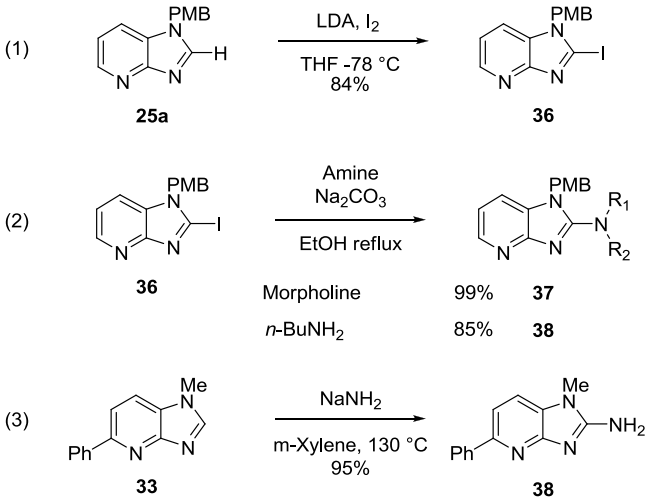


Scheme 9: Reaction Scope[a,b]

[a] Reaction Conditions: Pyr (0.4 mmol), Pd (0.004 mmol, 1 mol%), ligand (0.02 mmol, 5 mol %), 2 mL *t*-BuOH (0.2 M), 110 °C, 4 h. [b] Yields are of isolated products. [c] **L2** was used. [d] **L1** was used. [e] 2 h. [f] 0.5 h.

One advantage of this method is that C2 can be easily functionalized. The 2-position can be selectively deprotonated with LDA at low temperature, and subsequently quenched with

electrophiles.[64] (Scheme 10, eq. 1) We choose iodine as an electrophile to demonstrate the potential of this reaction which produced **36** in 84% yield. Further functionalization of **36** by S_NAr with amines as the nucleophiles illustrates the utility of our methodology for the synthesis of pentosidine (eq. 2).[65, 66] Alternatively, direct functionalization via Chichibabin amination[67, 68] was also performed to provide known mutagen 1-Me-5-PhIP **38**[69] from **33** in 95%. This route represents a short and high yielding synthesis of this naturally occurring N1 substituted imidazo[4,5-*b*]pyridine.



Scheme 10: Product Functionalization

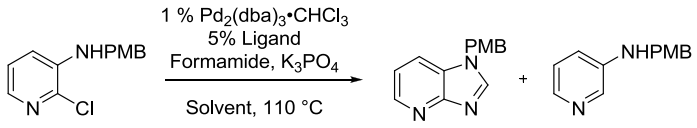
In summary, we have developed a regioselective palladium catalyzed method for the synthesis of imidazo[4,5-*b*]pyridines and imidazo[4,5-*b*]pyrazines. The current protocol is completely selective, and offers a high yielding route to regioisomers that are difficult to obtain using established methods. The present method is complementary to those developed by Buchwald[44] and Ma,[45] because N1 substituted isomers can now be obtained through metal catalyzed coupling.

2.3 SECOND GENERATION CONDITIONS

Imidazopyridines are a class of structures commonly used for pharmaceuticals and other uses.[37-39, 43, 70-73] One powerful method of preparing these structures is the palladium catalyzed coupling of an amide and a 3-amino-2-chloropyridine.[74] (*vida supra*) This method of preparing imidazo[4,5-*b*]pyridines and their derivatives, while useful, did not achieve all of our goals for their preparation. The goals of new catalytic reaction development are many; however, some of the more important are: high yield, low catalyst loadings, and readily available starting materials, including, the catalyst and ligands.[75, 76] In our quest to develop new reactions to produce imidazopyridines, we have achieved the first two objectives but the last remained elusive. Our previously published methodology to form imidazo[4,5-*b*]pyridines utilizes cheap and easily accessed 3-amino-2-chloropyridines, amides, with $Pd_2(dba)_3 \cdot CHCl_3$ as our precatalyst of choice.[74] However, the biaryl phosphine ligands used remained the limiting factor in scaling-up the reaction, creating logistical difficulties when this methodology was applied to the synthesis of pentosidine.[77] While significant progress has been achieved in addressing this problem;[78, 79] we nevertheless desired alternate reaction conditions that could make use of more readily available components, while retaining the high yields, ease of operation, and low catalyst loadings. Additionally, we desired to expand the reaction scope with regard to substrates and amide coupling partners.

In our initial report, we screened various ligands and observed that only biaryl ligands showed acceptable reactivity.[74] The non-proprietary ligand BippyPhos gave only a moderate yield; and the related 4-MeBippyPhos gave comparable yields to the biaryl ligands. However, the difficulty of preparing the 4-methylpyrazole, needed for the synthesis of the 4-MeBippyPhos, led us to explore other options. A survey of the literature revealed that Pd catalyzed C-N amide bond formation has been accomplished using Xantphos under in non-protic solvents.[19, 80-84] Further scrutiny of the literature revelaed an interesting trend, alcoholic solvents were best when ancillary ligands bearing a biarylphosphine motif were utilized; conversely, bidentate phosphine ligands required the use of aprotic solvents to have a positive outcome; with little to no conversion observed in alcoholic solvents.[9, 49, 51, 53, 74, 85] A reexamination of the reaction revealed that XantPhos and DPEPhos in aprotic solvents produced the desired cyclization product **25a** along with the reduced product **39**. (Entries 1-5, Table 3) This was confirmed by independently synthesizing the reduced product from 3-aminopyridine. Since **39** was not observed utilizing the biaryl ligands in *tert*-butanol we screened solvents to determine what, if any, affect the solvent had on the ratio of **25a** to **39**. No reaction was observed using DMF or NMP (Entries 6 and 7); while the reaction in diglyme showed moderate conversion, with no reduction observed. (Entries 8 & 9) These results combined with our previous success using *tert*-butanol suggested a protic solvent was critical to avoid or minimize formation of pyridine **39**. However, based on our previous data protic solvents interfered with the active palladium/ligand complex when bidentate ligands were utilized. To overcome these difficulties, we examined mixed solvent systems using an aprotic solvent and *tert*-amyl alcohol (*t*-AmOH).[86, 87, 88] The choice of alcohol was determined based on our previous results, and literature precedent demonstrating the effectiveness of a

binary solvent system.[54, 87, 89] First, mixtures of toluene and *t*-AmOH were examined. While excellent conversion was obtained in a 10:1 mixture, the reduced pyridine being the primary product. (Entries 10 & 11) Switching to the more polar 1,4-dioxane, which demonstrated promise as the sole solvent, we immediately observed positive a result. (Entries 12-14) In a 1:1 solvent mixture, XantPhos showed little change from solely 1,4-dioxane in entry 3; DPEPhos in a 10:1 mixture also displayed little change from entry 4. However, using XantPhos in a 10:1 solvent system we obtained a 93% yield in only six hours (Entry 14), as opposed to eighteen hours in solely 1,4-dioxane. (Entry 3) We also explored using BINAP under these solvent conditions, however after eighteen hours only 40% conversion was observed. (Entry 15) Other bidentate ligands, with bite angles similar to XantPhos (111°), such as dppb (99°) or dppf (96°) also proved inferior.[90] (Entries 16 & 17)



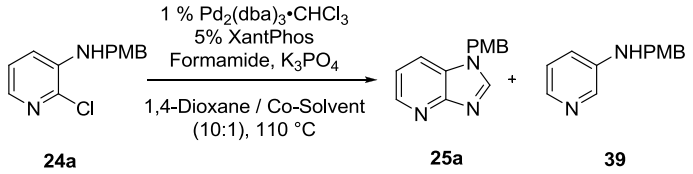
24a **25a** **39**

Entry	Ligand	Solvent	Yield (Reduced)[b]	Cnv.[b]	Rxn Time
1	XantPhos	t-BuOH	NR	-	18h
2	XantPhos	Toluene	22 (42)	79	18h
3	XantPhos	1,4-Dioxane	83 (15)	100	18h
4	DPEPhos	1,4-Dioxane	37 (46)	87	18h
5	XantPhos	DME	22 (31)	53	18h
6	XantPhos	DMF	NR	-	18h
7	XantPhos	NMP	NR	-	18h
8	DPEPhos	Diglyme	36 (0)	56	18h
9	XantPhos	Diglyme	33 (0)	51	18h
10	XantPhos	Toluene/t-AmOH (10:1)	11 (79)	100	6h
11	XantPhos	Toluene/t-AmOH (1:1)	13 (29)	42	6h
12	XantPhos	Dioxane/t-AmOH (1:1)	84 (0)	85	18h
13	DPEPhos	Dioxane/t-AmOH (10:1)	27 (35)	71	18h
14	**XantPhos**	**Dioxane/t-AmOH (10:1)**	**93%[c]**	**100**	**6h**
15	Rac-BINAP	Dioxane/t-AmOH (10:1)	4 (36)	40	18h
16	dppb	Dioxane/t-AmOH (10:1)	Trace (45)	48	18h
17	dppf	Dioxane/t-AmOH (10:1)	23 (19)	50	18h

Table 3 Reaction Optimization[a]

[a] Reaction Conditions: **24a** (0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (0.004 mmol, 1 mol %), ligand (0.02 mmol, 5 mol %), formamide (0.6 mmol), K_3PO_4 (0.6 mmol), solvent (0.2 M), 110 °C. [b]Using mesitylene as an internal standard. [c]Isolated Yield.

With the ligand and solvent mixture chosen, we explored alternatives to *tert*-amyl alcohol as the co-solvent to determine the effect on the reaction. (Table 4) Water resulted in rapid consumption of **25a**, however, soley the reduced pyridine **39** was observed. (Entry 2) Altering the co-solvent to methanol, provided some of desired imidazo[4,5-*b*]pyridine **25a**, but at greatly reduced conversion. (Entry 3) Swiching to the more hindered isobutanol and isopropanol offered a higher degree of conversion. (Entries 4 & 5) Isobutanol gave a 30% yield of **25a** with 20% **39**; while isopropanol provided 69% of **25a**, albeit at 78% conversion after 24h. Based upon these results, we posit that the reaction requires a sterically hindered protic co-solvent to give both high conversion of **24a** and to provide a high yield of the desired **25a**, while avoiding the formation of **39**.



Entry	Co-Solvent	Yield (Reduced)[b]	Conversion of **24a (%)**[b]
1	*t*-AmOH	93 (0)	100
2	H_2O	0 (74)	100
3	MeOH	13 (18)	31
4	*i*-BuOH	30 (20)	84
5	*i*-PrOH	69 (0)	78

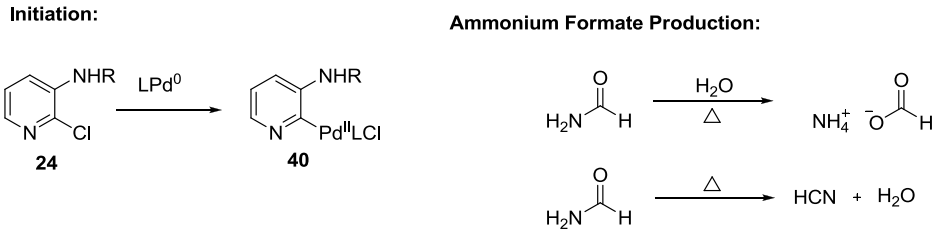
Table 4: Co-Solvent Screen[a]

[a] Reaction Conditions: **24a** (0.4 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.004 mmol, 1 mol %), ligand (0.02 mmol, 5 mol %), formamide (0.6 mmol), K_3PO_4 (0.6 mmol), solvent (0.2 M), 110 °C, 24h. [b]Using mesitylene as an internal standard.

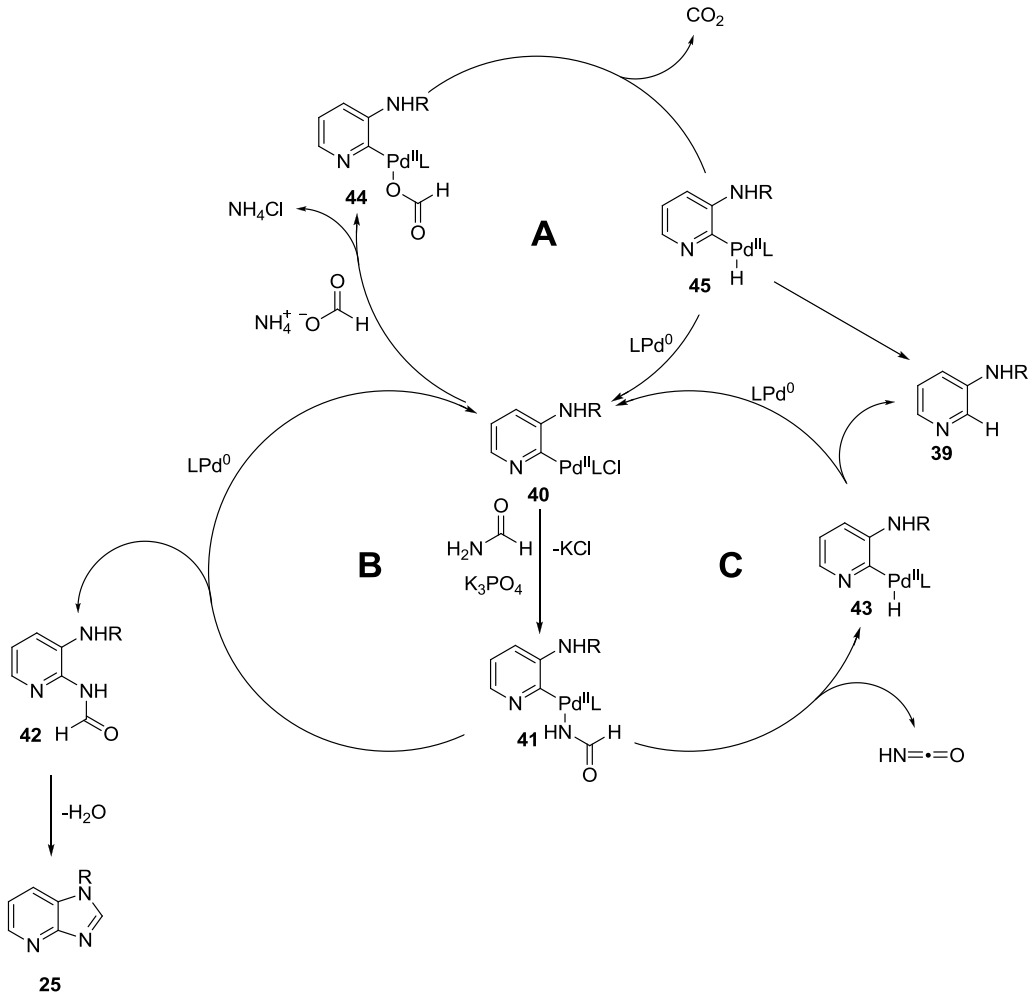
Mechanisticially, we believe there are a number of pathways operating under the reaction conditions. Our mechanisitic proposal begins with oxidative insertion of the zero-valent palladium into the pyridine-chlorine bond of **24** to give palladium (II) species **40**. (Scheme 11). Once this occurs, **40** can follow one of three distinct pathways, shown in scheme 12 as cycles **A**, **B** & **C**. Pathways **A** & **C** provide reduced pyridne **39**, while pathway **B** provides the desired imidazo[4,5-*b*]pyridine **25**. Since formamide is known to produce ammonium formate under aqueous conditions,[91, 92] we believe that pathway **A** is responsible for the reduction of pyridine **24a** when water was employed as the co-solvent. This distinct pathway would explain why **39** was the sole product when using water as a cosolvent. Formamide is also known to undergo dehydration to hygrogen cyanide and water, thereby providing a source of H_2O for non-aqueous conditions. Alternatively, advantageous water would explain the formation of **39** in some cases.

Pathways **B** & **C**, share the first step of ligand exchange to substitute the chlorine for formamide under base mediated conditions. Following this exchange, palladium (II) species can either undergo reductive-elimination to provide **42**, or β-hydride elimination to provide **43** and isocyanate. While uncommon, this β-hydride elimination is precedented at temperatures similar to our reaction conditions.[93, 94] Judging by the results of our optimization, there is a clear solvent effect for pathways **B** & **C**, although the exact mechanistic nature of this effect remains elusive. The ligand is also an important component, given the observed variation of **25** & **39** with alterations in the ancillary ligand. With conformationally constrained bulky ligands, such as the Buchwald ligands, the palladium may be unable to adopt the geometry for the β-hydride elimination process, thereby favoring pathway **B**.

In support of pathways **A** & **C** for the production of **25**, no reduced product was observed when amides other than formamide are used; suggesting that the hydride is derived from formamide. An experiment that could be conducted to support this hypothesis would be to utilize formamide-1-d_1, and observe if the deuterium is incorporated into the 2-position of **39**.

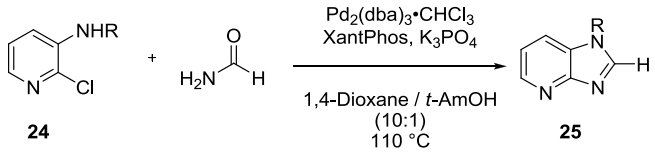


Scheme 11: Initiation & Ammonium Formation Production



Scheme 12: Mechanistic Hypothesis

With the new conditions in hand, we set out to explore the reaction scope. As shown in table 5, the new reaction conditions provided the desired imidazo[4,5-*b*]pyridines in good to excellent yields with substituted benzylic derivatives. (Entries 1-12) Electron-donating substituents (Entries 1-4) as well as halogenated substrates (Entries 5 & 6) performed well, giving 81 - 94% yields. Notably, under our previous conditions utilzing biaryl ligands, the *o*-chlorobenzyl subtrate was selectively coupled, but the *p*-chlorobenzyl system did not selectively couple. We observed multiple coupling events and a high degree of decomposition under previous conditions with the *p*-chlorobenzyl substrate. Under these modified conditions both the ortho and para chloro moities underwent clean cyclization giving 79 and 94% yield respectively. (Entries 7 & 8) Electron-neutral benzyl and biphenyl substrates were also well tolerated under the reaction conditions, and the chiral subtrate **25m** showed no racemization in addition to giving excellent yield. (Entries 9-11) One major improvement over the previous conditions was that electron deficient groups were tolerated under these more selective conditions, with **24t** giving a 95% yield, and the *m*-nitrobenzyl **24u** giving 57%. (Entries 12 & 13). Under the previously reported conditions, nitro groups proved deleterious giving decomposition and extremely poor yields. Aryl subsituents such as **24o** gave 94% yield. (Entry 14) *N*-Alkyl substrates performed well; although the more sterically bulky cyclohexylmethyl **24k** and cyclohexyl **24g** gave moderate 77% and 63% yields, respectively, while isopropyl gave 91%. (Entries 15 – 18)

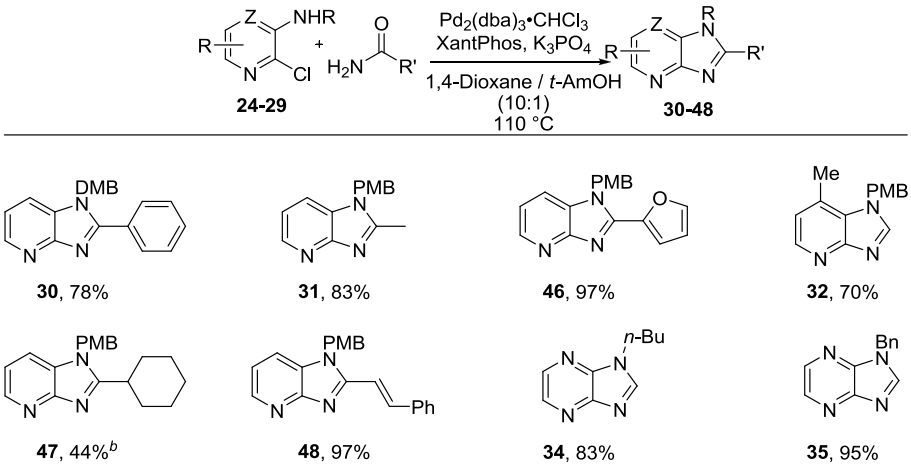


Entry	R	Yield (%)[b]	Product
1	$CH_2(4\text{-}OMeC_6H_4)$ **24a**	93	**25a**
2	$CH_2(2,4\text{-}OMeC_6H_3)$ **24c**	81	**25c**
3	$CH_2(2,5\text{-}OMeC_6H_3)$ **24q**	85	**25q**
4	$CH_2(4\text{-}Me_2NC_6H_4)$ **24r**	94	**25r**
5	$CH_2(3\text{-}FC_6H_4)$ **24d**	94	**25d**
6	$CH_2(4\text{-}FC_6H_4)$ **24v**	96	**25v**
7	$CH_2(2\text{-}ClC_6H_4)$ **24e**	79	**25e**
8	$CH_2(4\text{-}ClC_6H_4)$ **24s**	94	**25s**
9	$CH_2(4\text{-}PhC_6H_4)$ **24w**	70	**25w**
10	CH_2Ph **24b**	85	**25b**
11	*(R)*-$CH(CH_3)Ph$ **24m**	96	**25m**
12	$CH_2(4\text{-}CF_3C_6H_4)$ **24t**	95	**25t**
13	$CH_2(3\text{-}NO_2C_6H_4)$ **24u**	57	**25u**
14	Ph **24o**	94	**24o**
15	$CH_2(C_6H_{11})$ **24k**	77	**25k**
16	Cy **24g**	63	**25g**
17	Cyp **24j**	85	**25j**
18	*i*-Pr **24h**	91	**25h**

Table 5: Substrate Scope[a]

[a] Reaction Conditions: **24** (0.4 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.004 mmol, 1 mol %), XantPhos (0.02 mmol, 5 mol %), formamide (0.6 mmol), K_3PO_4 (0.6 mmol), solvent (0.2 M), 110 °C, 6.5h. [b] Isolated Yields.

One of our goals for the improvement of the reaction was to broaden the scope of amide coupling partners. Under our previous conditions we were able to utilize only benzamide and acetamide gave the desired imidazo[4,5-*b*]pyridines in 65% and 60% respectively. Using the new protocol **30** and **31** were obtained 78%, and 83% respectively. Previously no reaction or incomplete conversion was observed with cyclohexanecarboxamide and trans-cinnamide; however, 44% of **47** and 97% of **48** was acheived. 2-Furanamide also performs well, providing **46** in 97% yield. In contrast to the previously conditions, substitution at the four position of the pyridine slows the reaction, nevertheless, **32** was obtained in 70% yield. In agreement with our previous report, pyrazines performed well, giving **34** in 83% and **35** in 95% yield; again with reduced reaction times.



Scheme 13: Substrate Scope II[a]

[a] Reaction Conditions: Pyr (0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (0.004 mmol, 1 mol %), ligand (0.02 mmol, 5 mol %), Amide (0.6 mmol), K_3PO_4 (0.6 mmol), solvent (0.2 M), 110 °C. [b] Isolated as a mixture of **47** and Cyclohexanecarboxamide

In summary, we have developed conditions for the regioselective palladium-catalyzed synthesis of imidazo[4,5-*b*]pyridines and imidazo[4,5-*b*]pyrazines using XantPhos as a ligand. Additionally these conditions allow for the regioselective coupling of multiple-chlorinated substrates as well as electron-poor aryl functionality including a nitro-group. We were also able to utilize an expanded amide coupling-partner scope which can grant access to a large selection of C2 substituted imidazo[4,5-*b*]pyridines. We are currently working to expand this methodology to regioselectively couple polychlorinated aminopyridines.

3.0 SYNTHESIS OF 2-AMINO-IMIDAZO[4,5-*B*]PYRIDINES

3.1 INTRODUCTION

Guanidine containing molecules such as 2-aminobenzimidazole derivatives are an important class of heterocyclic compounds (Fig. 1).[95, 96] They have been utilized as organocatalysts for a variety of transformations including aldol[97] and Michael addition reactions.[98] These moieties also display a wide range of biological activities, most notably against multidrug-resistant bacteria.[99-104]

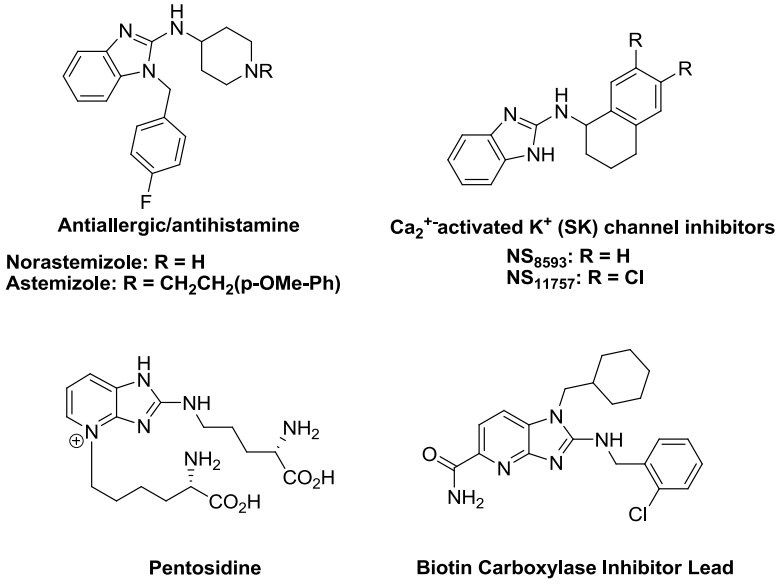
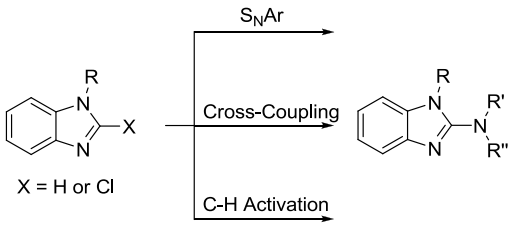


Figure 5: Biologically Active 2-Aminobenzimidazole/Azabenzimidazole

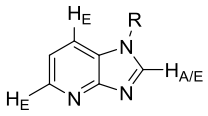
While the majority of these biological explorations have been carried out with 2-aminobenzimidazoles, Cheng and co-workers reported in 2009 that altering this scaffold from a benzimidazole to an imidazo[4,5-*b*]pyridine (4-azabenzimidazole) brings about a significant increase in biological activity.[105] Altering the benzene portion of benzimidazole by replacement with pyridine has profound effects on how these compounds interact with their environment. One of the more critical effects of this variation is increasing aqueous solubility, a major factor in determining how well a molecule can perform as a drug candidate.[106]

Introduction of an amino moiety at C2 is well precedented for benzimidazoles with several principal strategies for functionalization (Scheme 14). The simplest strategy is a direct nucleophilic aromatic substitution (S_NAr) of the corresponding halogenated benzimidazole.[107-110] Alternatively, the harsh conditions required for this transformation can in some cases be avoided through the use of palladium-catalyzed amination chemistry.[110-113] Finally a C-H activation strategy has been employed using selected nitrogen coupling partners.[114-117] However, application of these conditions to the corresponding imidazo[4,5-*b*]pyridine proved to be challenging.[77, 118]



Scheme 14: Functionalization Strategies

The copper catalyzed C-H activation conditions previously employed with benzimidazoles proved to be completely ineffective with imidazo[4,5-*b*]pyridines;[114-117] likely due to the strong coordination of N3 and N4 to copper.[119] Furthermore, palladium catalyzed methods resulted in poor to moderate yields of the desired product.[77] As shown in figure 6, imidazo[4,5-*b*]pyridines possess three electrophilic positions (H_E) that are difficult to regioselectively functionalize; but only one acidic site (H_A) which allows for selective derivatization.[120]



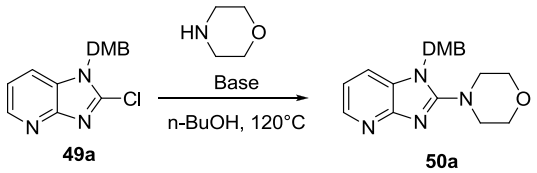
H_A = Acidic Position
H_E = Electrophillic Position

Figure 6: Reactive Sites on an Imidazo[4,5-*b*]pyridine

Failure of the aforementioned methods led us to pursue a more robust nucleophilic aromatic substitution strategy for introducing amine functionality at the imidazo[4,5-*b*]pyridine C2 position.[121-123] Chloroazoles were pursued as electrophiles because they have previously displayed superior reactivity compared to the corresponding iodoazoles.[77, 124, 125] The chloroazoles were conveniently prepared by deprotonation using LDA and quenching the anion with hexachloroethane to provide the 2-chloroazoles.[126, 127] This method allows for complete regioselective functionalization of the imidazo[4,5-*b*]pyridine and avoids the extremely harsh conditions and regioselectivity problems associated with the Chichibabin reaction or similar methodologies.[128, 129]

3.2 REACTION DEVELOPMENT

Optimization of the reaction parameters was conducted with 2,4-dimethoxybenyl substrate (**49a**) which has previously prepared in multigram batches.[77] A base screen was conducted with morpholine utilized as the nucleophile due to its availability, low volatility and known nucleophillicity. Inorganic bases such as sodium carbonate, sodium bicarbonate and potassium carbonate gave greater than 90% yields; sodium bases were found optimal giving yields of 97% (Table 1). Potassium bicarbonate gave a slightly inferior yield of 79%, while the less basic sodium acetate afforded only 55% of **50a**. Use of the soluble organic bases such as Hünigs base gave a moderate 73% yield **50a** and incomplete conversion.[109, 118]



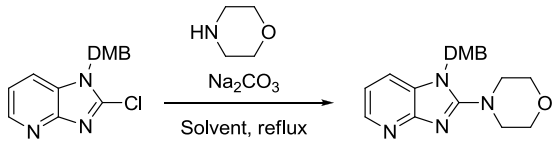
Entry	Base	Yield (%)[b]	Conversion (%)[b]
1	Na_2CO_3	97	100
2	$NaHCO_3$	97	100
3	K_2CO_3	90	100
4	$KHCO_3$	79	80
5	NaOAc	55	95
6	Et*N*-*i*-Pr_2	73	84

Table 6: Base Screen[a]

[a] Reaction conditions: **49a** (0.33 mmol), morpholine (0.40 mmol), Base (0.50 mmol), 0.66 mL *n*-BuOH, 120 °C, 16h [b] Using Mesitylene as an internal standard

A solvent screen was conducted in an attempt to optimize the reaction time (Table 2). Alcoholic solvents performed well with *n*-butanol being optimal with a reaction time of 16

hours. We found that lower boiling solvents (ethanol and isopropanol) were effective for the reaction giving greater than 90% yield of **50a**, but required 36 hours to reach completion (entries 2 and 3). Changing to 2-methoxyethanol gave 84% yield of **50a**. Ethereal solvents such as 1,2-dimethoxyethane (DME) and 1,4-dioxane gave 59% and 52% of **50a** respectively, although the reaction was incomplete even after 36 hours. Attempting to avoid the use of an additional base, we explored pyridine as both the base and the solvent; however, this gave an inferior yield and a large amount of decomposition was observed.



49a **50a**

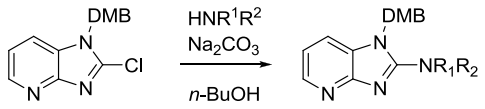
Entry	Solvent	Yield (%)[b]	Reaction Time (h)	Conversion (%)[b]
1	*n*-BuOH	97	16	100
2	EtOH	91	36	96
3	*i*-PrOH	90	36	90
4	2-Methoxyethanol	84	16	100
5	DME	59	36	91
6	1,4-Dioxane	52	36	90
7	Pyridine[c]	45	16	100

Table 7: Solvent Optimization[a]

[a] **49a** (0.33 mmol), morpholine (0.40 mmol), Na_2CO_3 (0.50 mmol), 0.66 mL solvent [b] using Mesitylene as an internal standard. [c] Reaction run without Na_2CO_3

With the optimized conditions in hand we explored the scope of this reaction with regard to the amino nucleophile (Table 8). In addition to morpholine, secondary amines such as piperidine, N,N-diethylamine and N,N-methylbenzylamine gave excellent yields: 94%, 85%, and 90% respectively (entries 2-4). Primary amines such as benzylamine (90%) and *n*-butylamine

(96%) also gave excellent yields (entries 5 and 6). As expected the reaction was sensitive to steric hindrance on the nucleophile. The bulky isopropylamine (entry 7) required 36 hours to reach full conversion and gave a 92% yield of **50g**; whereas *tert*-butylamine (entry 8) gave no conversion to **50h** even with extended reaction times. These trends are similar to those found in the fluoride mediated[107] and high-pressure S_NAr reactions[109] for the analogous benzimidazoles. When allyl amine was utilized, we obtained **50j** in 72% yield and no isomerisation of the olefin was observed in the crude proton NMR (entry 10). Chiral amines could also be utilized as shown in entries 11 and 12. No racemization was observed by chiral HPLC; although the increased steric environment on the nucleophile mandated a 24 hour reaction time for these substrates.



49a **50a - 50l**

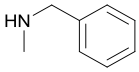
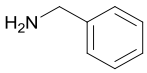
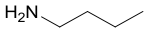
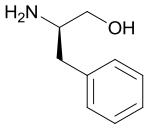
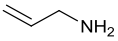
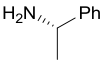
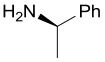
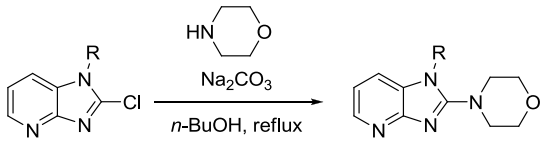
Entry	Amine	Yield (%) [b]	Product
1		97	**50a**
2		94	**50b**
3[c]		85	**50c**
4		90	**50d**
5		90	**50e**
6		96	**50f**
7[c]		92	**50g**
8[c]		NR	**50h**
9		51	**50i**
10		72	**50j**
11[d]		62	**50k**
12[d]		65	**50l**

Table 8: Amine Scope [a]

[a] Reaction conditions unless otherwise noted: **49a** (0.33 mmol), amine (0.40 mmol), Na_2CO_3 (0.50 mmol), 0.66 mL *n*-BuOH, 120 °C, 16h [b] Isolated yields [c] Reaction time: 36h. [d] Reaction time: 24h

The scope of N1 substitution on the azole was then explored to probe the effect on the S_NAr reaction (Table 4). Altering the dimethoxybenzyl moiety to *p*-methoxybenzyl or benzyl gave **51** and **52** in 86% and 74% yield, respectively (entries 2 and 3). Interestingly the *p*-fluorobenzyl system also gave a 77% yield of **53**, and no observable S_NAr chemisty occured on the benzyl group (entry 4).[130] Alkyl groups also performed well with cyclohexylmethyl (88%), isopropyl (79%), and neopentyl (62%) moieties giving the desired product in good to excellent yields (entries 5-7). The diminished yield of **56** is likely due to the close proximity of the neopentyl group to the reactive carbon which could impede formation of the tetrahedral Meisenheimer complex. The N-phenyl group was also well tolerated under the reaction conditions giving **57** in 82% yield (entry 8).



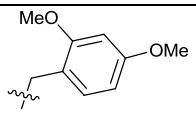
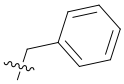
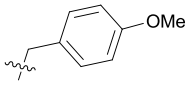
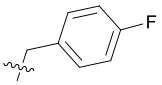
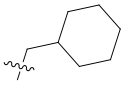
Entry	R	Yield (%) [b]	Product
1		97	**50a**
2		86	**51**
3		74	**52**
4		77	**53**
5		88	**54**
6		79	**55**
7		62	**56**
8		82	**57**

Table 9: Azole Scope [a]

[a] Reaction conditions unless otherwise noted: Azole (0.33 mmol), morpholine (0.40 mmol), Na_2CO_3 (0.50 mmol), 0.66 mL *n*-BuOH, 120 °C, 16h. [b] Isolated yields.

3.3 CONCLUSIONS

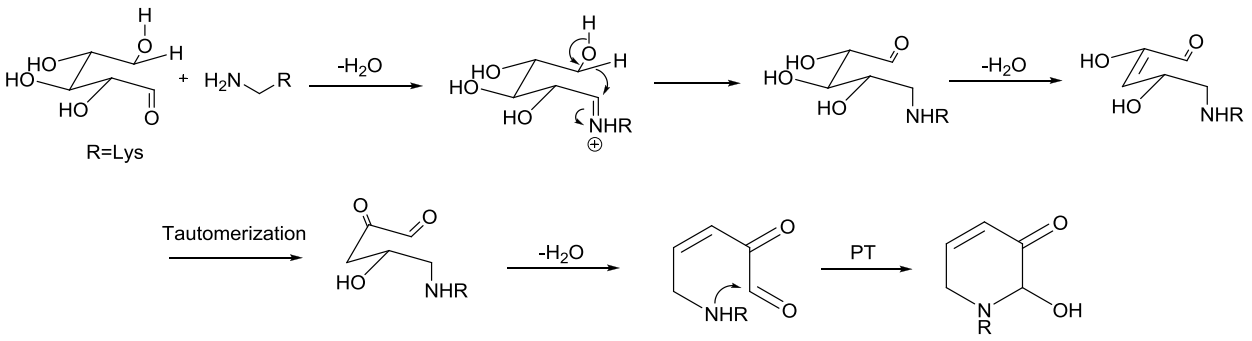
In summary, we have developed a facile and selective method for the amination of imidazo[4,5-*b*]pyridines which affords substituted 2-amino-imidazo[4,5-*b*]pyridines. This protocol is completely regioselective, procedurally simple, and provides rapid access to these

previously difficult to access moieties. Using this protocol both primary and secondary amines can be used as nucleophiles. 2-Chloro-imidazo[4,5-*b*]pyridines substituted at N1 with aryl, alkyl, and benzyl groups could be utilized as electrophiles and afford 2-amino-imidazo[4,5-*b*]pyridines. This protocol grants access to these molecules for future applications.

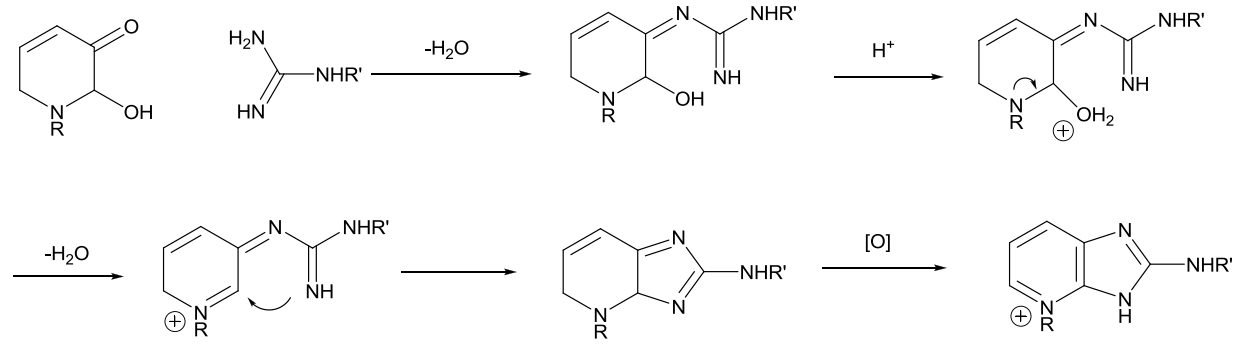
4.0 TOTAL SYNTHESIS OF PENTOSIDINE

4.1 BACKGROUND:

Pentosidine (**18**) is an advanced glycation endproduct (AGE) containing an imidazo[4,5-*b*]pyridine core that has attracted interest as a biochemical marker.[131] It was discovered as an extracellular protein crosslink by Monnier in 1989, and is one of only a handful of characterized AGEs.[132] Pentosidine is a naturally occuring biological fluorophore, and as such has found use in non-invasive diagnostics. It has been reported as a chemical marker of diabetic complications, kidney dysfunction, oxidative stress, aging and age-related diseases.[133-140] Recently, Veralight Inc. has begun marketing a device that utilizes the spectroscopic properties of AGEs to carry out a non-invasive method of detecting type II diabetes.[141-144] Biosynthetically, pentosidine is believed to be a protein cross-link derived from a post-translational Maillard reaction of arginine and lysine residues with a pentose (ribose shown).[145] (Schemes 15 & 16)



Scheme 15: Proposed Biosynthesis of Pentosidine I



Scheme 16: Proposed Biosynthesis of Pentosidine II

There is also recent evidence that pentosidine is both a singlet oxygen sensitizer and an antioxidant.[146, 147] Pentosidine is available commercially, however its low supply and corresponding high price make it difficult to study.[148] Therefore, we sought to develop a straightforward route to pentosidine that would allow us to explore the properties of this molecule.

From a synthetic point of view pentosidine (**18**) presents an interesting structural target. The imidazo[4,5-*b*]pyridine core has attracted casual interest in the literature, with few direct efforts at preparation.[41-43, 71, 74, 149-152] The challenges inherent in this molecular architecture are

derived from the need to generate this moiety in a cost efficient and chemically straightforward manner.

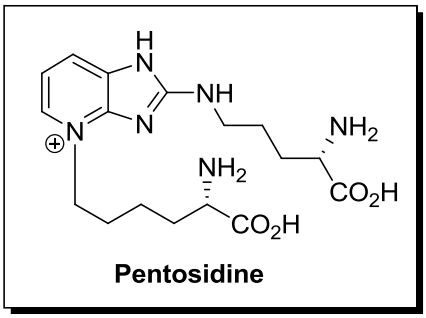
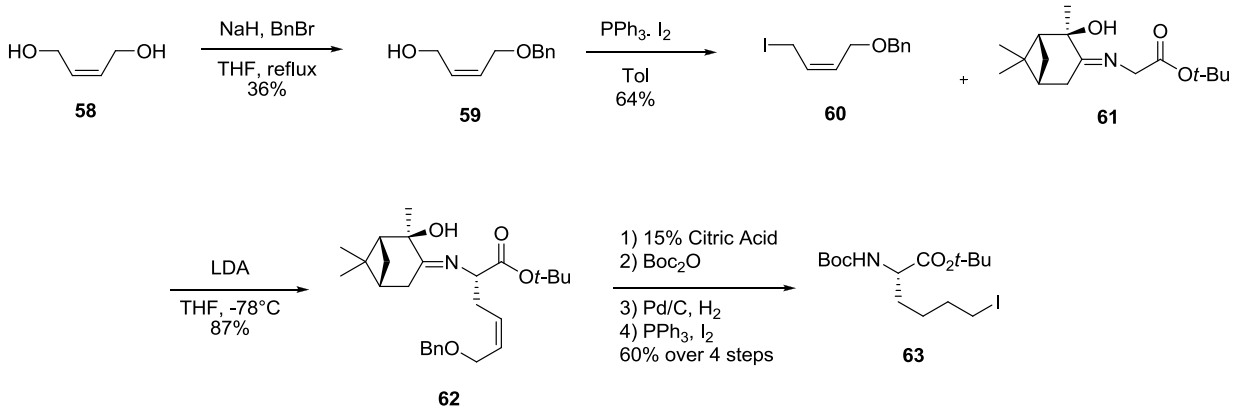


Figure 7: Pentosidine

4.1.1 Previous Syntheses

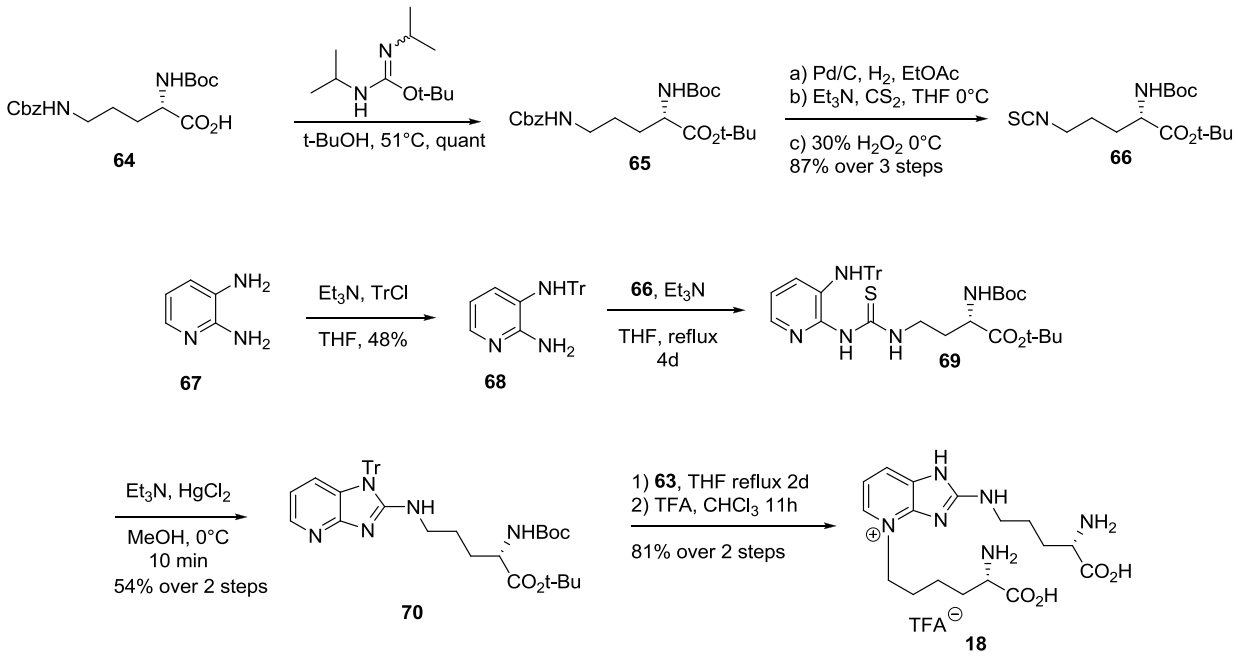
There have been three published syntheses of Pentosidine to date. The first was published in 1989 and is not a total-synthesis, but a one-step biomimetic synthesis.[132] Sell and Monnier simply mixed the biological starting materials (arginine, lysine and ribose) while heating in an aqueous environment and purified the mixture via HPLC to give 0.02% yield of pentosidine. While this method of production has the advantage of utilizing very cheap starting materials, the yield and tedious purification, do not lend themselves to large scale production. Their synthesis does, however, help to support the proposed biological pathway to pentosidine.[145] More recently Cravotto and co-workers have improved upon this method, increasing the yield to 8%.[153] This was accomplished by using Nα-Boc protected amino acids in the presence of $Ba(OH)_2$ in DMF; followed by TFA deprotection. However this route also required HPLC purification and the use of microwave technology makes this route impractical for large scale production.

The first total-synthesis of pentosidine was published by Shioiri and co-workers in 1991[48, 154] with 9 steps in the longest linear sequence giving a 15% yield, and 15 total steps. Utilizing a pinene derived chiral auxiliary **61** to create side-chain iodide **63** over 7 steps. (Scheme 17)



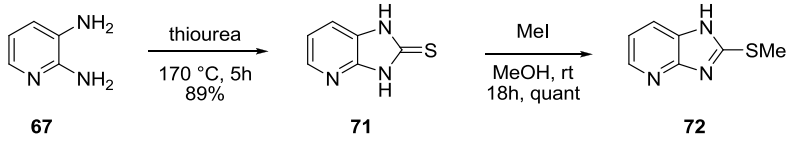
Scheme 17: Preparation of Iodide 63

The imidiazo[4,5-*b*]core core of the molecule was derived from 2,3-diaminopyridine (**67**) which is quite expensive (> $10/g). The first step of their synthesis was a selective trityl-protection which proceeds in moderate yield, and was further elaborated onto the imidazo[4,5-*b*]pyridine core using a guanylation with thioisocyanate **66** and cyclized using stoichiometric mercury (II) chloride giving imidazo[4,5-*b*]pyridine **70** in moderate yield. The synthesis was completed by regioselective alkylation of the nucleophillic pyridine nitrogen with iodide **63**, and subsequent global deprotection to give pentosidine as its TFA salt.



Scheme 18: Shioiri's Endgame

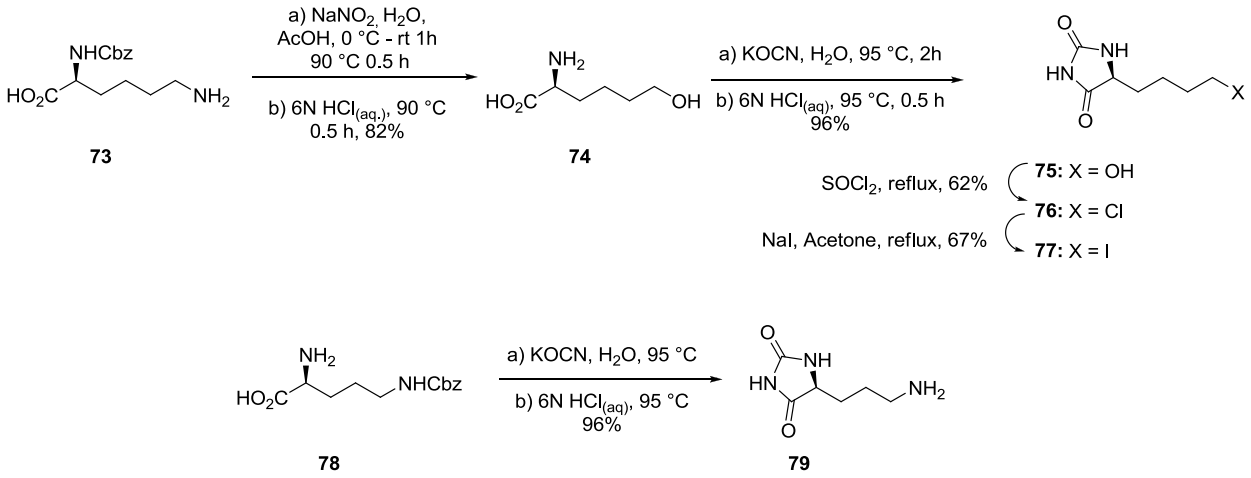
More recently Sayre's group published their approach and total-synthesis of pentosidine.[155, 156] Their approach also starts from 2,3-diaminopyridine (**67**) to provide heterocycle **72** over 2 steps in excellent yield. (Scheme 19)



Scheme 19: Preparation of Imidazo[4,5-*b*]pyridine 72

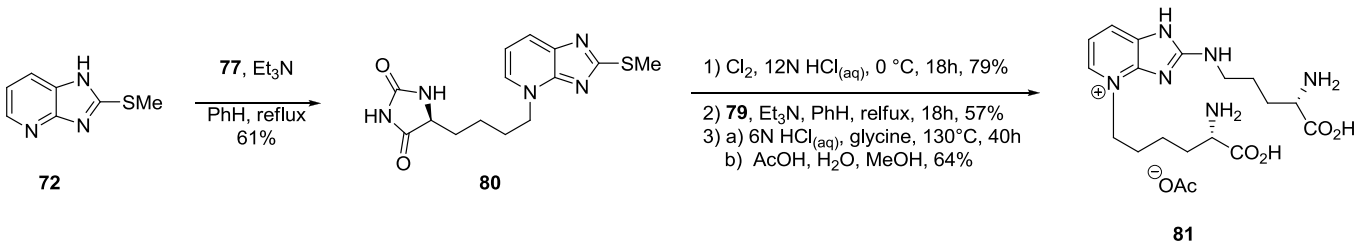
Sayre derived the two chiral centers present in the natural product from their parent amino acids. Iodide **77** was synthesized from Nα-Cbz-Lysine by diazotization of the unprotected

amine, substitution with water and acidic hydrolysis of the Cbz group to give **74**. The amino acid was protected using the Urech hydantoin synthesis[157] and the terminal alcohol was subsequently converted into iodide **77** in two steps. Ornithine **79** was prepared by N_{δ}-Cbz-ornithine **78** in a similar fashion. (Scheme 20)



Scheme 20: Sayre's Side-Chain Synthesis

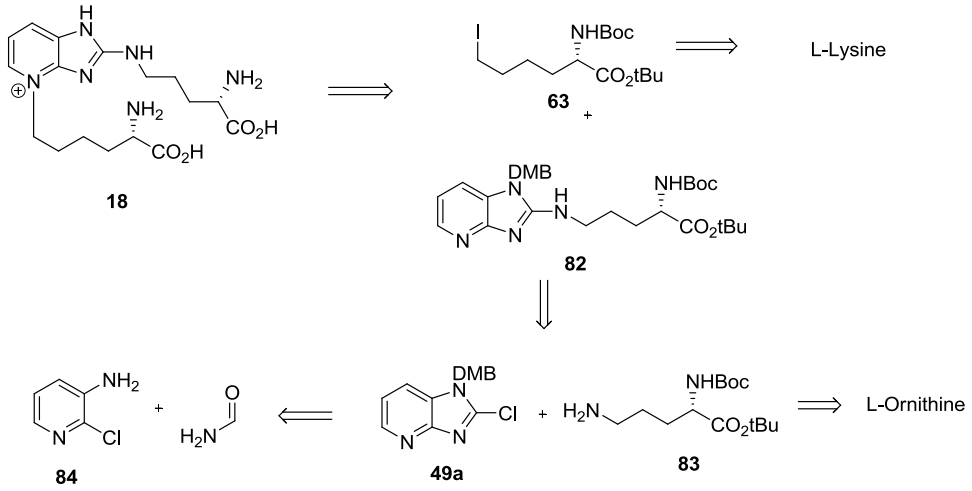
The total synthesis was completed by alkylation of the pyridine nitrogen with iodide **77**, chlorination of the sulfide, S_NAr of the resulting choride with amine **79**, and deprotection of the hydantoins under thermal acidic conditions in the presence of glycine. This produces the hydrochloride salt of pentosidine which was exchanged for the acetate during purification. This synthesis is a short seven linear steps with a yield of 5.7%. However, the low yield is misleading because only three steps are outside the longest linear sequence, all of which are high yielding; as opposed to Shioiri's synthesis where multiple low yielding steps are not part of the longest linear sequence.



Scheme 21: Sayre's Endgame

4.2 RETROSYNTHESIS:

Retrosynthetically we envisioned disconnections at C2 and N4, leaving an imidazo[4,5-*b*]pyridine core with an electron-donating protecting group at N1. This protection scheme is required so that N4 will be activated for selective alkylation. Without N1 or N3 blocked, a mixture of N1, N3 and N4 alkylation products is obtained.[41] Additionally, Shioiri demonstrated that electron-withdrawing groups deactivated the imidazo[4,5-*b*]pyridine for alkylation at any position.[48] These disconnections would allow the introduction of protected ornithine and lysine residues, thus avoiding asymmetric reactions and chiral auxiliaries by generating the stereocenters from the chiral pool. Utilizing a cross-coupling / cyclization strategy for the preparation of imidazo[4,5-*b*]pyridines allows use of 3-amino-2-chloropyridine as our starting material.[74] (*vida supra*) Using this route, we would avoid using 2,3-diaminopyridine which is problematic to functionalize in a regioselective manner.[48, 154, 158]

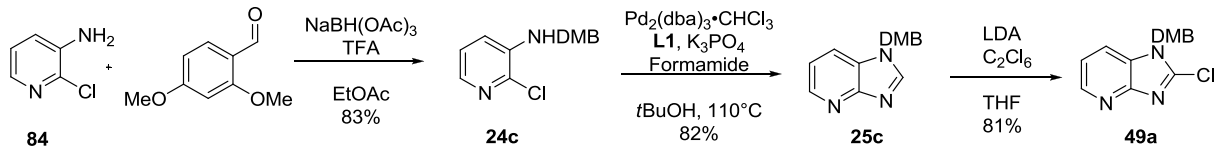


Scheme 22: Retrosynthetic Analysis

4.3 FORWARD SYNTHESIS

4.3.1 Core Synthesis

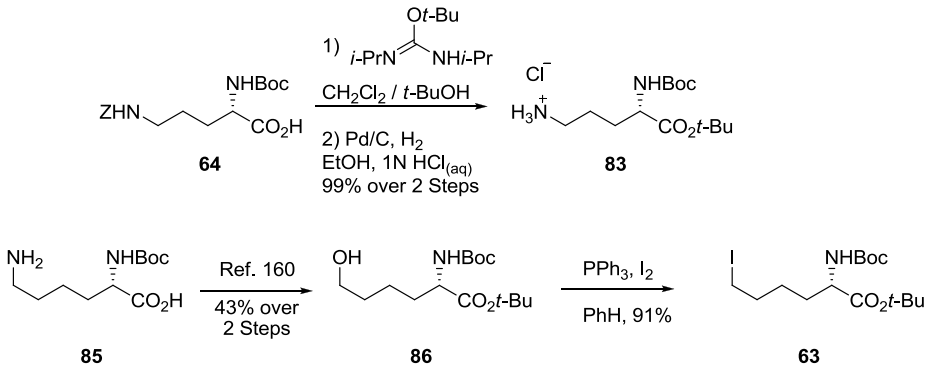
Our synthesis commenced with commercially available amino-2-chloropyridine **84**,[159] which was protected as its 2,4-dimethoxybenzyl (DMB) amine (**24c**) via a reductive amination.[50, 158] This protecting group was chosen carefully with three important requirements: 1) be electron-donating, 2) easily removable, ideally under acidic conditions for a global deprotection, 3) installed in one-step from 3-amino-2-chloropyridine. The 2,4-dimethoxybenzyl group fulfils all of these requirements. As a benzyl group it was electron-donating, it can be deprotected by acid, and it can be installed using the previously demonstrated reductive amination methodology. *(vida supra)* We then applied our palladium-catalyzed amide coupling/cyclization methodology to generate the core imidazo[4,5-*b*]pyridine in a single operation.[74] High yields have consistently been obtained for this reaction on 2.5 - 5 gram scale. Compound **25c** was chlorinated at the 2-position using hexachloroethane & LDA, giving chloro-azole **49a** in 81% yield.[126] This three-step sequence rapidly assembles the activated imidazo[4,5-*b*]pyridine core in high yield on gram scale. (Scheme 23)



Scheme 23: Pentosidine Core Synthesis

4.3.2 Side Chains

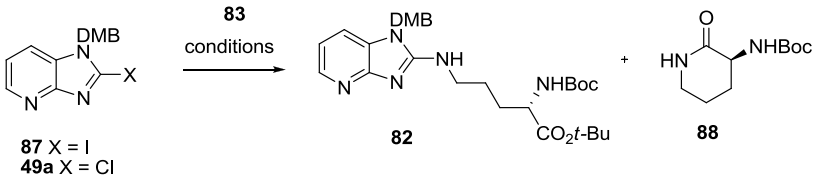
Ornithine residue **83** was prepared in excellent yield from commercially available Boc-Orn(Z)-OH, by esterification with an isourea followed by Cbz cleavage with Pd/C and H_2. (Scheme 24) The lysine fragment can be prepared from Boc-Lys(H)-OH via alcohol **86** using the method of Adamczyk.[160] Alcohol **86** was then transformed to the desired iodide under Appel conditions in 91% yield. This short, two step route avoids the seven step sequence pursued by Shioiri. In addition the stereocenter was installed from commercially available lysine **85**.[48, 154]



Scheme 24: Side Chains

4.3.3 Functionalization of C2

Functionalization of C2 with the ornithine side-chain **83** proved unexpectedly complicated. (Table 10) We first explored palladium catalyzed methods developed by Senanayake for the synthesis of the 2-aminobenzimidazole, Norastemizole.[110, 112] Unfortunately, only low yields of the desired product **83** were obtained (entries 1-5). Having previously reported C2 functionalization using an S_NAr reaction with an iodide analogous to **87**, we returned to this for installation of the ornithine residue.[74] Initial attempts proved unsatisfactory due to the propensity of ornithine **83** to cyclize and form δ-lactam **88** (entry 6).[161] Switching to DMF as the solvent resulted in the dimethylamine adduct as the only isolable addition product (entry 7). The halide was modified from iodine to the more electronegative chlorine **49a** to increase the reactivity of the azole for nucleophilic attack. Use of **49a** combined with excess ornithine **83** led to formation of desired product **82** in 87% yield (entries 8 and 9). Efforts to lower the equivalents of ornithine **83** using either fluoride[107] or DABCO[162-164] as nucleophilic catalysts did not improve the yield or selectivity (entries 10 and 11). Using this optimized procedure, we were able to synthesize >1g of **82** in a single campaign.



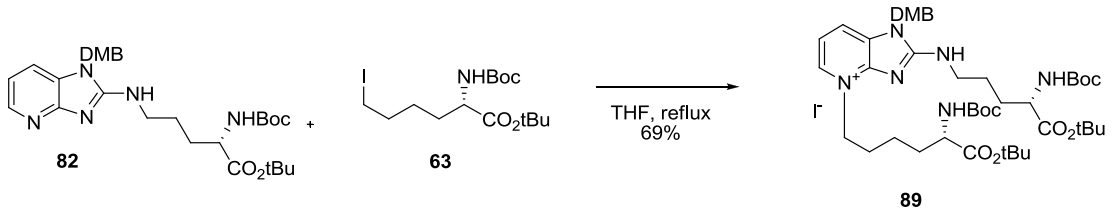
entry	X	conditions[c]	solvent	yield (%)	**82**:**88**
1	I	A	toluene	10	1:0
2	I	B	*t*-AmOH	0	-
3	Cl	A	toluene	13	1:0
4	Cl	B	*t*-AmOH	39	1:1
5	Cl	B	toluene	44	2:1
6	I	C	EtOH	0	-
7	I	C	DMF	0[d]	-
8[a]	Cl	D	EtOH	31	2:1
9[a]	Cl	D	*n*-BuOH	87	1:0[b]
10	Cl	E	TGME	0	-
11	I	F	DMA	0	-

Table 10: Orn Installation

[a]2.0 Equivalents Orn. [b]After purification, 1:1 ratio prior to purification. [c]Conditions A: 1.5 mol % $Pd_2(dba)_3$, 4.5 mol % BINAP, NaO*t*-Bu, reflux. Conditions B: 1.5 mol % $Pd_2(dba)_3$, 4.5 mol % BippyPhos, K_3PO_4, reflux. Conditions C: Na_2CO_3, reflux. Conditions D: $EtN(iPr)_2$, reflux. Conditions E: KF, 2,6-lutidine, 120 °C. Conditions F: cat. DABCO, Na_2CO_3. [d]Dimethylamine addition observed

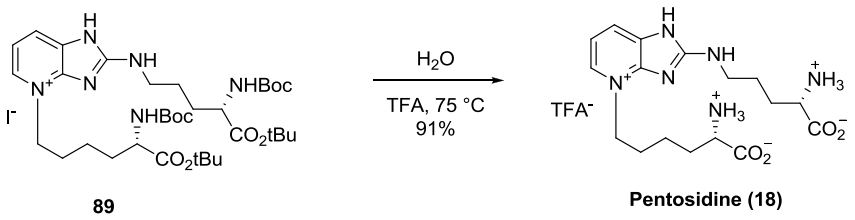
4.3.4 Endgame

As aforementioned, electron-donating substituents installed at C2 and N1 activate N4 for alkylation. Iodide **63** and imidazo[4,5-*b*]pyridine **82** were refluxed in THF to provide iodide salt **89**, the fully protected pentosidine. Purification of pyridinium salts are known to be problematic;[165] however, to our delight, **89** was purified using standard silica gel chromatography.[166]



Scheme 25: Installation of Lysine Side Chain

With protected pentosidine in hand, all that remained was the deprotection of various protecting groups, including: *N*-Boc, *tert*-butyl ester, and the dimethoxybenzyl group. By design these groups were removed under acidic conditions, although the DMB group required a cation scavenger such as triethylsilane or H_2O to intercept the resulting benzyl cation and prevent reversion to the protected starting material. Heating the reaction in 10:1 TFA / H_2O for 48h proved to be the most effective protocol, allowing for a simple reverse-phase silica gel plug as purification to give the trifluoroaceate salt of the natural product in 91% yield. Following this protocol, pentosidine (**18**) was obtained as the TFA salt without the need for tedious HPLC purification.[167] In our hands, we were able to prepare 112 mg of pentosidine in a single-campaign over the six step sequence.



Scheme 26: Global Deprotection

In summary, we accomplished a short, rapid total synthesis of pentosidine that utilizes a highly efficient synthesis of imidazo[4,5-*b*]pyridine **25c**. Use of economical S_NAr and alkylation chemistry allows for a scalable and reproducible synthetic route. This approach provides pentosidine with only six steps in the longest linear sequence (ten total steps) in 30.1% yield. The high efficiency of the synthesis, low-cost of the starting materials, and absence of toxic reagents makes this a practical method for research scale synthesis of pentosidine, thereby allowing further studies of this interesting natural product.

5.0 SYNTHESIS OF IMIDAZO[4,5-*C*]PYRIDINES

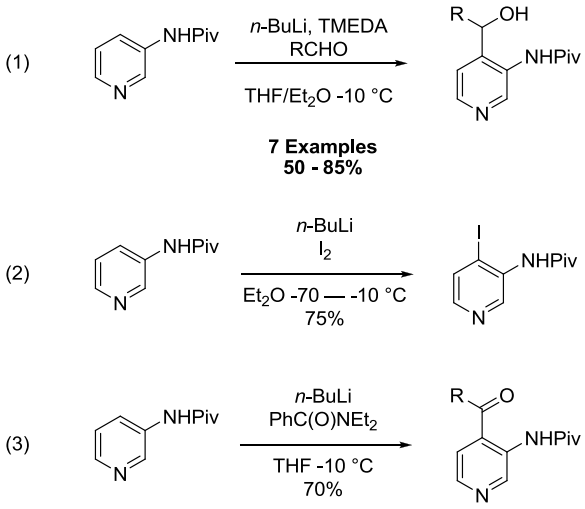
The imidazo[4,5-c]pyridine scaffold is an important pharmacophore which has proven to be useful for a number of biologically relevant targets.[29, 168-176] Previously these compounds have been prepared from the relevant diaminopyridines; however these compounds are difficult to obtain due to problematic regioselective functionalization.

We recently published a new route for the preparation of imidazo[4,5-*b*]pyridines (IMPs), utilizing an amide cross-coupling strategy and starting from inexpensive and readily available 3-amino-2-chloropyridine.[74] This strategy also allows for the regioselective synthesis of the N1 substituted IMPs with either alkyl or aryl substitution at the two position. Based upon the success of this approach, we explored the cooresponding 3-amino-4-chloropyridines for the formation of desirable imidazo[4,5-*c*]pyridines; this approach would provide access to these heterocycles that are difficult to access by other means.

Unfortunately, although the 3-amino-2-chloropyridines, are easily functionalized by reductive amination[50] and Chan-Lam techniques [59, 60], the corresponding 3-amino-4-chloropyridine failed to provide the desired products under identical reaction conditions. Due to these unforseen difficulties, as well as the cost and availability of 3-amino-4-chloropyridine, we elected to investigate 3-aminopyridine as an entry to these systems. Of note, commercial 3-

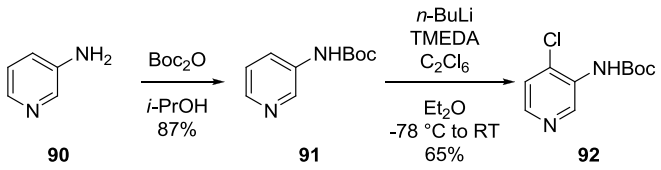
amino-4-chloropyridine rapidly decomposed under ambient storage conditions, yielding an unknown insoluble byproduct, even after purification.

Functionalization of 3-aminopyridines at the 4 position is well known using directed metallation chemistry.[177-182] (Scheme 27) While the majority of this work has been carried out using the pivaloyl amide, we elected to utilize the *tert*-butoxycarbamate (Boc) due to the ease of removal after the desired transformation.



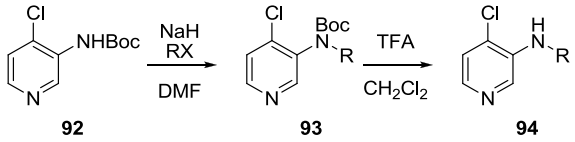
Scheme 27: Pivaloyl Directed Functionalizations

Protection of 3-aminopyridine has traditionally been carried out under basic conditions, however, this leads to a mixture of the mono and bis Boc protected aminopyridine.[183] To avoid this issue we elected to employ an alternative procedure utilizing only Boc anhydride in aqueous isopropanol, which gave **91** in 87% yield.[184] The chloro substituent was installed using Kelly's metallation protocol and utilizing hexachloroethane as the electophillic chlorine source.[126]



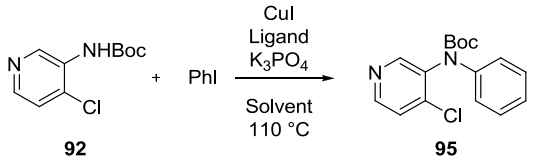
Scheme 28: Synthesis of 3-Bocaminio-4-chloropyridine

With the desired 4-chloropyridine in hand, we focused on installing the desired functionality on the N3 nitrogen. Alkyl & benzyl moieities were installed from **92** with sodium hydride and the relevent alkyl or benzyl electrophile followed by removal of the Boc group with TFA to give compounds **94a** – **94c**. (Scheme 29)



Scheme 29: Alkylations

However, installation of aryl and heteroaryl functionality by this strategy would not be practical, and an alternative approach was explored. One possibility was to use a palladium catalyzed reaction, however, due to the aryl chloride present in our substrate we dismissed this strategy due to competitive coupling events. Copper-catalyzed couplings were examined to avoid these problems. Basic pyridines are known to interfere with these reactions, and pyridine itself is occasionally used as a ligand.[185] However, despite these potential difficulties, we surmised copper-catalyzed conditions could be developed which would afford the desired products.

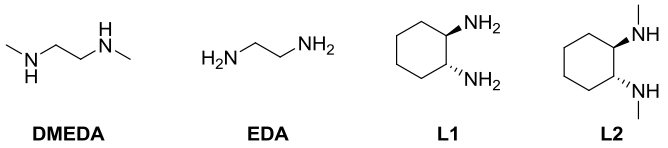


92 **95**

Entry	Ligand	Solvent	Conversion[b] (%)	Yield[b] (%)
1	DMEDA	DMF	100	0
2	DMEDA	Tol	100	0
3	DMEDA	Dioxane	79	43
4	EDA	Dioxane	71	59
5	**L1**	Tol	70	65
6	**L1**	**Dioxane**	**100**	**96[c]**
7	**L2**	Dioxane	72	trace
8[d]	**L1**	Dioxane	100	65
9[e]	**L1**	Dioxane	77	74
10[f]	**L1**	Dioxane	19	19

Table 11: Copper Catalyzed Amidation Optimization

[a] Reaction Conditions: 10 mol% CuI, 20 mol% Ligand, 2 Eq. Base, 0.5 M. [b] Using mesitylene as an internal standard [c] Isolated yield [d] 20 mol% CuI, 40 mol% Ligand [e] Cs_2CO_3 used as the base [f] K_2CO_3 used as the base. DMEDA = *N*,*N'*-Dimethylethylenediamine. EDA = Ethylenediamine. **L1**= (+/-) *trans*-1,2-Diaminocyclohexane. **L2** = (+/-) *N*,*N'*-Dimethyl-1,2-diaminocyclohexane.

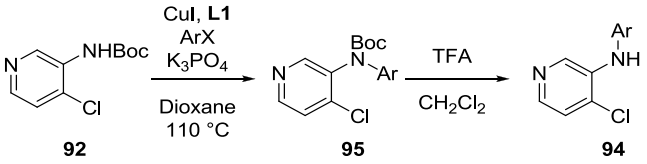


DMEDA **EDA** **L1** **L2**

Figure 8: Diamine Ligands

Exploration of this reaction commensed with copper (I) iodide and diamine ligands commonly used for copper-catalyzed amidation.[186-189] (Table 11) No activity was observed using *N*,*N'*-Dimethylethylenediamine (DMEDA) in either DMF or toluene; 79% conversion and 43%

yield was obtained in 1,4-dioxane. (Entries 1-3) Ethylenediamine (EDA), a more unencumbered ligand, gave 71% conversion and an increased 59% yield. (Entry 4) The more rigid *trans*-1,2-diaminocyclohexane gave similar moderate results when the reaction was carried out in toluene, when 1,4-dioxane was utilized complete conversion and 96% isolated yield was obtained. (Entries 5 & 6) The more electron-rich *N,N'*-dimethyl analog **L2** gave moderate conversion (72%) but only trace product. This result supports Buchwald's hypothesis that the coupling of sterically bulky secondary amides are aided by unencumbered diamine ligands.[187, 188] (Entry 7) Attempts to further improve the coupling to shorten the reaction time, and further improve the yield by changing the base or increasing the catalyst loading were unsuccessful. (Entries 8-10)



92 **95** **94**

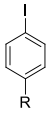
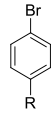
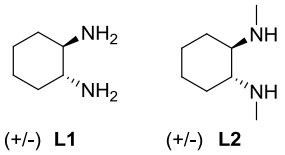
Entry	ArX	Yield of Amidation[b] (%)	Yield of Deprotection[b] (%)
			
1	R = H	96	97
2	R = Me	76	92
			
3[d]	R = OMe	30	83
4[d]	R = C(O)Me	90	89
5[d]	R = CN	84	71
6[d]	R = CF_3	79	89
7		97	96
8		-	54[c]
9		-	58[c]

Table 12: Copper-Catalyzed Amidation Scope[a]

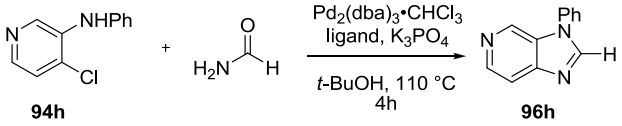
[a] Reaction Conditions: 1) 10 mol% CuI, 20 mol% **L1**, 2 Eq. K_3PO_4, 1,4-Dioxane (0.5 M); 2) 25% TFA in CH_2Cl_2 . [b] Isolated Yield [c] Over two steps. [d] Reaction Performed by Robert Wilson



(+/-) **L1** (+/-) **L2**

Figure 9: Diamine Ligands

With amidation conditions in hand, we explored the substrate scope of this reaction. (Table 12) As shown previously, iodobenzene performed in excellent 96% yield, intermiediate **95h** was deprotected under acidic conditions to provide **94h** in 97% yield. (Entry 1) 4-Iodotoluene gave 76% and 92% respectively for the amidation and deprotection sequence. (Entry 2) Aryl bromides were also effective under the reaction conditions. Electron-rich 4-bromoanisole, gave only 30% yield for the amidation. (Entry 3) Electron-poor aryl bromides bromoacetophenone, benzonitrile and benzotrifluoride all gave good to excellent yields. (Entries 4-6) Both five and six-membered heterocycles undergo amidation under the optimized conditions, with 2-bromopyridine giving an excellent 97% yield. (Entry 7) 2-Bromothiophene and 3-bromothiophene coupled effectively, although full conversion was not observed, thus the mixture was subjected to deprotection conditions and the yield was obtained over the two step sequence. (Entries 8 & 9)



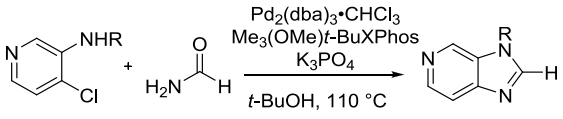
Entry	Ligand	Conversion (%)[b]	Yield(%)[b]
1	Me_3(OMe)*t*-BuXPhos	100	90[c]
2	cBRIDP	100	81
3	BippyPhos	100	87
4[d]	TrippyPhos	10	trace
5[d]	RuPhos	15	0
6[e]	(*t*-Bu_3PH)BF_4	17	0
7[e]	(Cy_3PH)BF_4	18	0
8[e]	XantPhos	17	0

Table 13: Pd-Catalyzed Cyclization Optimization[a]

[a] Reaction Conditions: **94h**, Pd (1 mol %), ligand (5 mol %), 1.5 eq. Formamide, 0.2 M *t*-BuOH, 110 °C, 4 h. [b] Using mesitylene as an internal standard. [c] Isolated yield. [d] Reaction carried out by Robert Wilson. [e] Reaction carried out by Lauren Kaminsky.

With ample amounts of the desired 3-amino-4-chloropyridine substrates, we moved onto the dehydrative cyclization chemistry. (Table 13) Utilizing 3-phenylamino-4-chloropyridine (**94h**) as a test substrate under conditions analogous to those used for the 3-amino-2-chloropyridines.[74] The newly developed Me_3(OMe)*t*-BuXPhos[78] ligand was utilized in place of previously employed Me_4*t*-BuXPhos or *t*-BuBrettPhos ligands, due to availability. This ligand performed well in the amidation / cyclization sequence, giving the desired imidazo[4,5-*c*]pyridine in 90% yield. The cBRIDP[190] ligand developed by Takasago and Singer's BippyPhos[54] also gave complete conversion to the desired imidazo[4,5-*c*]pyridine **96h**, with

slightly reduced yields. TrippyPhos[89] gave only trace product, while RuPhos, tri-*tert*-butylphosphine, tricyclohexylphosphine, and XantPhos all displayed no reactivity.



Entry	R	Yield (%)[b]	Product
1	$CH_2(C_6H_5)$ **94a**	84	**96a**
2	CH_2(2,5-OMe-C_6H_3) **94b**	85	**96b**
3[d]	CH_2(3,5-OMe-C_6H_3) **94c**	52	**96c**
4[c]	CH_2(4-F-C_6H_4) **94d**	75	**96d**
5[c]	CH_2(4-Ph-C_6H_4) **94e**	75	**96e**
6[c]	Me **94f**	58	**96f**
7	*n*-Pr **94g**	85	**96g**
8	Ph **94h**	90	**96h**
9[c]	4-OMePh **94i**	80	**96i**
10[c]	4-MePh **94j**	89	**96j**
11[c]	4-CF_3Ph **94k**	91	**96k**
12[c]	4-C(O)Me **94l**	87	**96l**

Table 14: Imidazo[4,5-*c*]pyridine Reaction Scope

[a] Reaction Conditions: **94** , Pd (1 mol %), ligand (5 mol %), 1.5 eq. Formamide, 0.2 M *t*-BuOH, 110 °C, 4 h. [b] Isolated yield. [c]Reaction carried out by Robert Wilson. [d] Reaction carried out by Lauren Kaminsky.

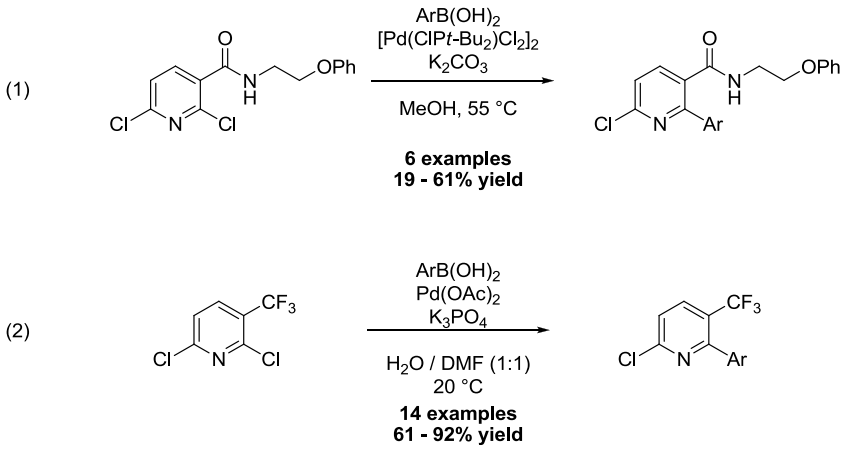
With the reaction optimization complete, attention was turned to examining the reaction scope. As shown in table 14, the reaction provided the desired imidazo[4,5-*c*]pyridines in moderate to excellent yields. Benzyl derivitives performed well; with electron-donating, electron-withdrawing, arly and fluorine substitution tolerated under the reaction conditions.

(Entries 1-5) Methyl and *n*-propyl substitution performed well giving 58% and 85% yields respectively. (Entries 6 & 7) The aryl substituted derivatives provided the cyclized products in excellent 80 – 91% yields, with both electron-poor and electron-rich aryl systems performing admirably. (Entries 8 -12)

In summary, we have developed copper-catalyzed conditions for the amidation of 3-NBoc-4-chloropyridine with aryl and heteroaryl halides to provide monoarylated 3-amino-4-chloropyridines after subsequent deprotection. This methodology, does not react with chloro functionality on the pyridine leaving it available for subsequent reactions, such as our palladium catalyzed amidation / cyclization methodology to produce imidazo[4,5-*c*]pyridines.

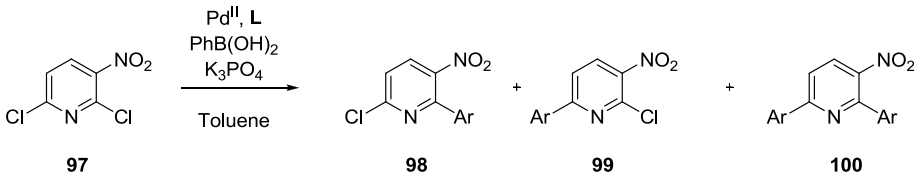
6.0 REGIOSELECTIVE AMIDATION OF POLYCHLORINATED AMINOPYRIDINES

Polysubstituted pyridines and pyridine derivatives are found in many natural products, pharmaceutical motifs as well as other useful systems.[191-194] Palladium catalyzed cross-coupling using polyhalogenated pyridines would provide a straightforward entry into these valuable systems, provided it could be done regioselectively. Previously, we have successfully carried out a Suzuki coupling at the six position 3-Boc(methyl)amino-6-bromo-2-chloropyridine, and there have been many reported examples of chemoselective reactions.[58, 195, 196] Some progress on this front has been reported recently in the literature, with Yang and co-workers using an amide as a directing group for a palladium catalyzed Suzuki coupling.[197] (Scheme 30, eq. 1) Yang obtained poor to moderate yields with regioselectivities ranging from 4:1 to 15:1. More recently, Langer and co-workers have published the regioselective Suzuki coupling of 2,6-dichloro-3-trifluoromethylpyridine with a sub-stoichiometric amount of boronic acid; obtaining complete regioselectivity and good to excellent yields.[198] (Scheme 30, eq. 2)



Scheme 30: Directed Suzuki Couplings

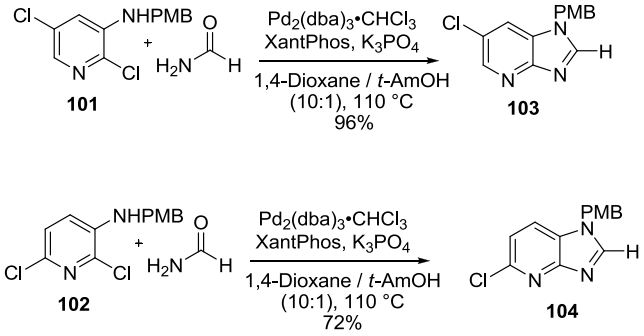
Another attempt at a regioselective palladium catalyzed Suzuki coupling of a 2,6-dichloro-3-nitropyridine utilized a ligand based approach.[199] However, although preference for the two-position was observed, the major product observed was the bis-arylated product when two equivalents of the boronic acid was used. When only one equivalent of the boronic acid was utilized, the preference for the C2 coupled product was pronounced, with up to a 73% yield of **98**, although C6 and bis-coupled products were also observed.



Scheme 31: Suzuki Coupling of 2,6-Dichloro-3-nitropyridine

Previously, we had observed regioselective Buchwald-Hartwig amidation under our newly developed XantPhos conditions with 2-chloro-N-(4-chlorobenzyl)pyridin-3-amine (**24s**).

(*vida supra*). One of our objectivies in our reexamination of imidazopyridines synthesis was to utilize polychlorinated pyridines, providing the desired imidazopyridines with additional functional handles. To our delight when **101** & **102** were subjected to the reaction conditions we observed a regioselective coupling event. As illustrated in scheme 32, the 3-amino-2,5-dichloropyridine **101** was selectively coupled to give **103** in excellent yield. The corresponding 2,6-dichloro species also was selectively coupled, giving **104** in 72% yield.



Scheme 32: Regioselective Amidation

The selectivity in the 2,5-dichloropyridine, easily rationalized by examining bond-dissociation energies (BDEs).[200] The two-position has a 2.8 kcal/mol lower BDE than the five-position. Other methods of determining which halogen will react first have been developed, but all reinforce the reactivity of the two-position over the five-position.[201, 202] Choice of ligand and solvent have also been shown to effect which site reacts first in other systems.[195, 196, 203]

While the 2,5-dichloro system performs well, the corresponding 2,6-dichloropyridine fails to react completely under the conditions. We observed no products arising from a coupling event at the six-position, however the reaction only proceeded to 75% conversion. Calculations

indicate that the BDE difference between the two and six positions is minimal, with the six position favored by 0.2 kcal / mol. This suggests that the regioselective coupling could be directed by the amino functionality, transforming a functional group that normally interferes with reactivity to a directing group.[204]

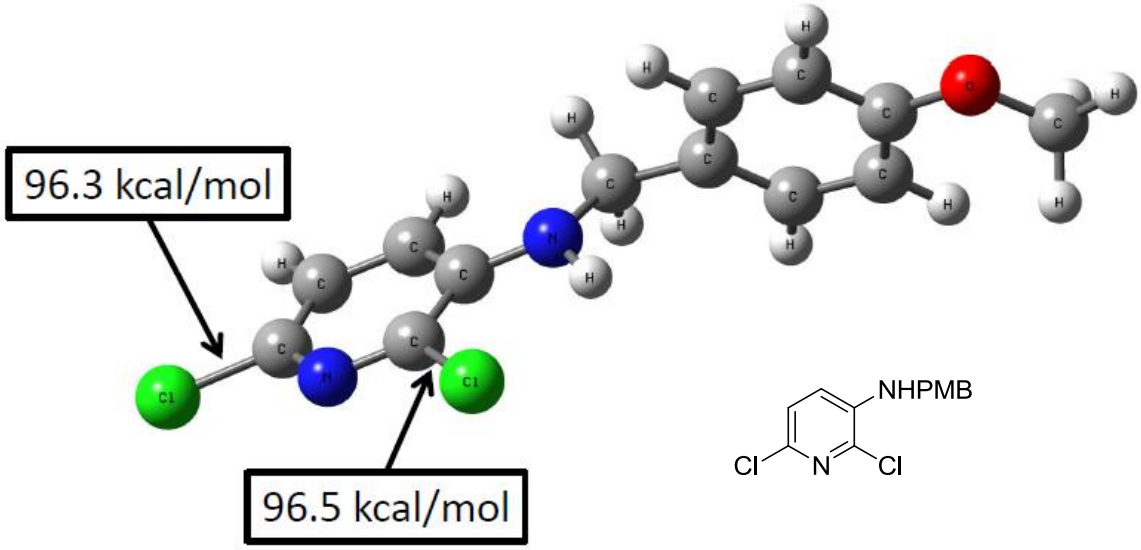
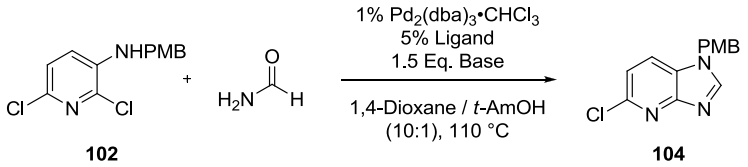


Figure 10 : BDE Calculations

(Calculations conducted by Tom Juliano, Korter Group, Syracuse University)

We then proceeded to perturb the conditions in an effort to improve the efficiency of the reaction, while maintaining the high degree of regioselectivity. (Table 15) Increasing the catalyst and ligand loading proved detrimental to the reaction. (Entry 3) Increased reaction time did not substantially improve the yield. (Entry 4) In an effort to improve the solubility of the base, and before we discovered that the byproduct was reduction of the chloropyridine, we added water to the reaction; although this produced what we believe is 5-amino-2-chloropyridine. (Entries 5-7) Altering the ligand proved to be quite detrimental to the reaction, giving reduced conversion and

an increased amount of the reduced product. (Entries 8 – 14). However, the closely related DPEPhos gave complete conversion, prompting a further exploration with both XantPhos and DPEPhos. (Entry 15) Altering the solvent mixture ratio allowed for complete conversion with both XantPhos and DPEPhos, although the result was an increase in the reduced product's yield. (Entries 16 -20) Changing the base also proved ineffectual. (Entries 21 – 23)



102 **104**

Entry	Ligand	Base	Rxn. Time	Conversion (%)[h]	Yield (Reduced) (%)[h]
1	XantPhos	K_3PO_4	6.5 h	75	72[i]
2	XantPhos	K_3PO_4	8 h	80	74[i]
3[a]	XantPhos	K_3PO_4	7 h	57	49
4	XantPhos	K_3PO_4	22 h	83	76
5[b]	XantPhos	K_3PO_4	6 h	100	52 (43)
6[c]	XantPhos	K_3PO_4	18 h	100	45 (47)
7[d]	XantPhos	K_3PO_4	18 h	100	34 (36)
8	dppf	K_3PO_4	18 h	67	34 (24)
9	dppb	K_3PO_4	18 h	44	Trace (44)
10	(*t*-Bu)$_3$PHBF$_4$	K_3PO_4	18 h	7	0 (Trace)
11	Cy_3PHBF_4	K_3PO_4	18 h	13	0 (13)
12	dppm	K_3PO_4	18 h	25	0 (25)
13	dppe	K_3PO_4	18 h	40	0 (40)
14	*Rac*-BINAP	K_3PO_4	18 h	25	12 (Trace)

15	DPEPhos	K_3PO_4	18 h	100	58 (24)
16[e]	DPEPhos	K_3PO_4	7 h	100	73 (22)
17[f]	DPEPhos	K_3PO_4	7 h	100	78 (21)
18[g]	DPEPhos	K_3PO_4	7 h	100	63 (25)
19[f]	XantPhos	K_3PO_4	7 h	80	52 (34)
20[g]	XantPhos	K_3PO_4	7 h	53	40 (12)
21	XantPhos	NaO*t*-Bu	18 h	100	29 (24)
22	XantPhos	Cs_2CO_3	7 h	100	72 (23)

Table 15: Dichloropyridine Reaction Optimization

[a] 2% $Pd_2(dba)_3 \cdot CHCl_3$, 10% ligand. [b] 5 Eq. H_2O. [c] 1 Eq. H_2O. [d] 0.5 Eq. H_2O. [e] Run in 4:1 (Dioxane:*t*-AmOH). [f] 2:1 [g] 1:1. [h] Using mesitylene as an internal standard. [i]Isolated Yield, Unknown Yield of Reduced Product

In summary, we have discovered reaction conditions for the regioselective amidation of polychlorinated aminopyridines to provide the chlorinated imidazo[4,5-*b*]pyridines. Further exploration of the reaction conditions and substrate will be carried out to improve this reaction by minimizing the formation of the reduced byproducts and increasing the yield. Additional explorations will also determine the substrate scope of this reaction.

7.0 APPENDEX I: EXPERIMENTALS

7.1 GENERAL EXPERIMENTAL

GENERAL PROCEDURES: Unless otherwise indicated, all reactions were conducted in oven- (140°C) or flame-dried glassware using distilled and degassed solvents under positive pressure of dry argon with standard Schlenk techniques. All air-sensitive reagents were stored in an MBraun labmaster glovebox containing dry argon gas. Dry tetrahydrofuran (THF), toluene, acetonitrile (CH_3CN), and methylene chloride (DCM) were obtained by passing commercially available pre-dried, oxygen-free formulations through two activated alumina columns using an MBraun MB-SPS solvent purification system. Stainless steel syringes or cannulae that had been oven-dried (140°C) and cooled under an argon atmosphere or in a desiccator were used to transfer air- and moisture-sensitive liquids. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on precoated glass plates of silica gel (0.25 mm) 60 F_{254} from EMD Chemicals Inc. using the indicated solvent system. Visualization was accomplished with ultraviolet light (UV 254 nm), or by shaking the plate in a sealed jar containing silica gel and Iodine. Alternatively, plates were treated with one of the following solutions (this was accomplished by holding the edge of the TLC plate with forceps or tweezers

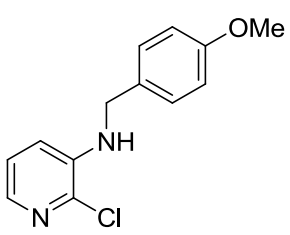
and immersing the plate into a wide-mouth jar containing the desired staining solution) and carefully heating with a hot-air gun (450°C) for approximately 1-2 min (NOTE: excess stain was removed by resting the TLC on a paper towel prior to heating): 10% phosphomolybdic acid in ethanol, 1% potassium permanganate/7% potassium carbonate/0.5% sodium hydroxide aqueous solution, and/or anisaldehyde in ethanol with 10% sulfuric acid. Flash column chromatography was performed using Silia Flash® P60 silica gel (40-63 μm) from Silicycle. All work-up and purification procedures were carried out with reagent grades solvents (purchased from VWR) in air.

INSTRUMENTATION: Infrared (IR) spectra were recorded on a Thermo Nicolet IR-100 spectrometer, ν_{max} in cm^{-1}, and were obtained from samples prepared as thin films between NaCl plates. ^{1}H NMR spectra were recorded on a Bruker Avance DPX-300 (300 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) and are calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity, coupling constants (Hz), and integration. The following abbreviations or combinations thereof were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, pent = pentet, sext = sextet, sept = septet, m = multiplet, at = apparent triplet, aq = apparent quartet, br = broad. ^{13}C NMR spectra were recorded on a Bruker Avance DPX-300 (75 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm and are calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: δ 77.16 ppm). ^{19}F NMR spectra were recorded on a Bruker Avance DPX-300 (282.4 MHz) spectrometer. Chemical shifts are reported in ppm and are calibrated using solvent as an

external reference ($CFCl_3$: δ 0.00 ppm). High resolution mass spectra (HRMS) were performed at the mass spectrometry facility of CUNY Hunter College (New York, New York), or SUNY Buffalo (Buffalo, New York) or Old Dominion University (Norfolk, VA). Enantiomeric ratios were determined by chiral high performance liquid chromatography (HPLC) analysis on a Varian Prostar instrument using chiral analytical columns as stated, in comparison with authentic racemic samples. Optical rotations were measured at a sodium D line (589 nm) on a Rudolph Research Analytical Autopol III polarimeter and reported as follows: $[\alpha]_D^T \lambda$ (c in g/100 mL), in the designated reagent grade solvent. Melting points (m.p.) are uncorrected and were recorded using an Electrothermal Mel-Temp® melting point apparatus. Elemental Analyses were performed on a Costech ECS 4010 elemental analyzer with a thermal conductivity detector and 2 meter GC column maintained at 50°C.

7.2 1ST GENERATION

Reductive Amination General Procedure[50]:



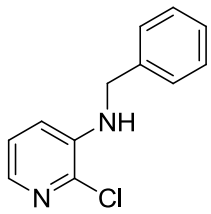
2-Chloro-N-(4-methoxybenzyl)pyridin-3-amine (24a)[50]

To a flame-dried 250 mL RBF was added 3-amino-2-chloropyridine (5.0 g, 38.89 mmol), 60 mL EtOAc and *p*-Methoxybenzaldehyde (5.18 mL, 42.78 mmol). The mixture was allowed to stir until complete dissolution (about 5 min) at which time trifluoroacetic acid (5.77 mL, 77.78 mmol) was added as a single portion via syringe and the reaction mixture immediately turned yellow. After stirring at rt for 2 min sodium triacetoxyborohydride was added in two equal portions 1 minute apart. After 30 min the reaction was judged complete by TLC and quenched by the addition of 20% $NaOH_{(aq)}$ (30 mL); the pH was adjusted to 8 by addition of $NaOH_{(s)}$ (50 pellets). The layers were then separated and the organic layer was washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a blue tinged solid which was recrystallized with 40 mL of 3:1 EtOAc : Hexanes to give 9.64 g (99%) of colorless cubes.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.71 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.03 (dd, *J* = 8.1 Hz, 4.5 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.84 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 4.75 (br s, 1H), 4.31 (d, *J* = 5.4 Hz, 2H), 3.81 (s, 3H)

MP: 90 – 91 °C

R_f (20% EtOAc / Hexanes): 0.24



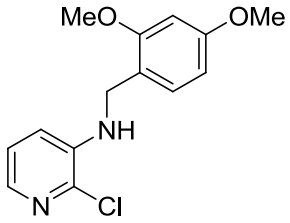
N-Benzyl-2-chloropyridin-3-amine (24b)[50]

Following the general procedure, 3-amino-2-chloropyridine (2.0 g, 15.56 mmol), 120 mL EtOAc, benzaldehyde (1.74 mL, 17.11 mmol), trifluoroacetic acid (2.31 mL, 31.11 mmol) and sodium triacetoxyborohydride (3.95 g, 18.67 mmol) were combined and stirred for 15 minutes. The reaction was quenched with 20% $NaOH_{(aq)}$ and the pH was adjusted with $NaOH_{(s)}$ (20 pellets). The layers were separated, the organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude **24b** which was recrystallized from 14 mL of 1:1 Hexanes:EtOAc to give **24b** as a colorless cubes (2.5 g, 74%)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.72 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 7.41 – 7.27 (m, 5H), 7.03 (dd, *J* = 7.8 Hz, 4.5 Hz, 1H), 6.83 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 4.84 (br s, 1H), 4.41 (s, 2H)

MP: 76 – 77 °C

R_f (20% EtOAc / Hexanes): 0.23



2-Chloro-N-(2,4-dimethoxybenzyl)pyridin-3-amine (24c)

Following the general procedure, 3-amino-2-chloropyridine (10.0 g, 77.8 mmol), 120 mL EtOAc, 2,4-dimethoxybenzaldehyde (14.2 g, 85.6 mmol), trifluoroacetic acid (11.6 mL, 17.7 mmol) and sodium triacetoxyborohydride (19.8 g, 93.3 mmol) were combined and stirred for 60 minutes. The reaction was quenched with 20% $NaOH_{(aq)}$ and the pH was adjusted with $NaOH_{(s)}$ (70 pellets). The layers were separated, the organic layer was washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 18.7 g of crude **24c** which was recrystallized from 80 mL of 2:1 Hexanes:EtOAc to give **24c** as a pale green crystalline solid (15.15 g, 70%)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.69 (d, *J*= 3 Hz, 1H), 7.14 (d, *J*= 8.1 Hz, 1H), 7.04 (ddd, *J*= 8.1, 4.8, 0.6 Hz, 1H), 6.90 (dd, *J*= 8.1, 1.5 Hz, 1H), 6.48 (d, *J*= 2.4 Hz, 1H), 6.43 (dd, *J*= 8.1, 2.4 Hz, 1H), 4.82 (at, *J*= 5.1 Hz, 1H), 4.30 (d, *J*= 5.7 Hz, 2H), 3.85 (s, 3H), 3.80 (s, 3H)

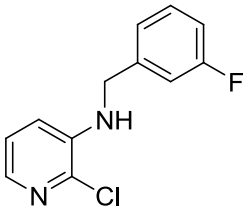
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 160.6, 158.5, 141.0, 137.3, 136.3, 129.4, 123.4, 118.1, 118.0, 104.0, 98.8, 55.5, 55.4, 42.5

FT-IR: (NaCl, thin film) ν = 3423, 2937, 2836, 1614, 15841505, 1463, 1289, 1207, 1156, 1035 cm^{-1}.

HRMS (ESI) Calc ($C_{14}H_{15}ClN_2O$): 278.0825, Found: 278.0822

MP: 56-58 °C

R_f (20% EtOAc / Hexanes): 0.23



2-Chloro-N-(3-fluorobenzyl)pyridin-3-amine (24d)

Following the general procedure, 3-amino-2-chloropyridine (2.0 g, 15.56 mmol), 24 mL EtOAc, 3-fluorobenzaldehyde (1.81 mL, 17.12 mmol), trifluoroacetic acid (2.31 mL, 31.12 mmol) and sodium triacetoxyborohydride (3.96 g, 18.67 mmol) were combined and stirred for 30 minutes. The reaction was quenched with 20% $NaOH_{(aq)}$ and the pH was adjusted with $NaOH_{(s)}$ (20 pellets). The layers were separated, the organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 3.24 g of crude **24d** which was recrystallized from 10 mL of 1:1 Hexanes:EtOAc to give **24d** as a white crystalline solid (2.41 g, 66%)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.74 (dd, *J*=1.8 Hz, 4.8 Hz, 1H), 7.36-7.29 (m, 1H), 7.12 (d, *J*=7.8 Hz, 1H), 7.06-6.95 (m, 3H), 7.78 (dd, *J*=1.2 Hz, 7.8 Hz, 1H), 4.89 (s, 1H), 4.42 (d, *J* = 5.7 Hz, 2H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 164.7, 161.4, 140.5 (d, J_{C-F} = 25.4 Hz), 140.2, 137.0, 136.7, 130.3 (d, J_{C-F} = 30.5 Hz), 123.3, 122.4 (d, J_{C-F} = 10.7 Hz), 117.9, 114.0 (dd, J_{C-F} = 169 Hz, 78.8 Hz), 46.6 (d, J_{C-F} = 6.2 Hz),

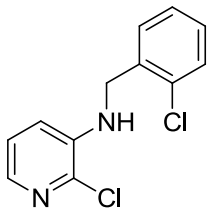
^{19}F NMR (282.4 MHz, CDCl3) δ= -112.81 (dt, *J*= 9.0 Hz, 6.0 Hz)

FT-IR: (NaCl, thin film) ν = 3430, 3064, 2916, 2850, 1586, 1490, 1325, 1251, 1102, 1056, 784 cm^{-1}.

HRMS (ESI) Calc ($C_{12}H_{11}ClFN_2O$): 237.0589, Found: 237.0588

MP: 93-95 °C

R_f (20% EtOAc / Hexanes): 0.25



2-Chloro-N-(2-chlorobenzyl)pyridin-3-amine (24e)

Following the general procedure 3-amino-2-chloropyridine (2.0 g, 15.56 mmol), 24mL EtOAc, 2-chlorobenzaldehyde (1.92 mL, 17.11 mmol), trifluoroacetic acid (2.31 mL, 31.11 mmol) and sodium triacetoxyborohydride (3.95 g, 18.67 mmol) were combined and stirred for 30 minutes. The reaction was quenched with 20% $NaOH_{(aq)}$ and the pH was adjusted with $NaOH_{(s)}$ (20 pellets). The layers were separated, the organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give a white solid which was recrystallized from 45 mL of 2:1 Hexanes:EtOAc to give **24e** as colorless cubes (3.73 g, 87%)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.73 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.34 – 7.30 (m, 1H), 7.29 – 7.19 (m, 2H), 7.04 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 6.78 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 4.94 (br s, 1H), 4.51 (d, *J* = 6 Hz, 2H)

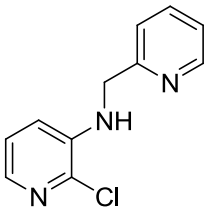
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 140.3, 137.2, 137.0, 135.0, 133.3, 129.9, 128.9, 128.5, 127.2, 123.5, 118.0, 45.1

FT-IR (NaCl, thin film) ν = 3428, 3063, 2929, 1585, 1564, 1492, 1443, 1386, 1325, 1055 cm^{-1}.

HRMS (ESI) Calc ($C_{12}H_{11}N_2Cl_2$): 253.0294, Found: 253.0291

MP: 85 – 86 °C

R_f (20% EtOAc / Hexanes): 0.38



2-Chloro-N-(pyridin-2-ylmethyl)pyridin-3-amine (24f)

Following the general procedure 3-amino-2-chloropyridine (1.0g, 7.78 mmol), 12mL EtOAc, 2-pyridine carboxaldehyde (0.81 mL, 8.56 mmol), trifluoroacetic acid (1.2 mL, 15.6 mmol) and sodium triacetoxyborohydride (1.98 g, 9.34 mmol) were combined and stirred for 30 minutes. The reaction was quenched with 20% $NaOH_{(aq)}$ and the pH was adjusted with $NaOH_{(s)}$ (20 pellets). The layers were separated, the organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give of **24f** as brown viscous oil, which was used without further purification (1.63 g, 95%)

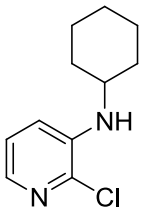
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.61 (ddd, *J* = 4.8 Hz, 1.5 Hz, 0.9 Hz, 1H), 7.73 (dd, *J* = 4.8 Hz, 1.8 Hz, 1H), 7.67 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.33 - 7.19 (m, 1H), 7.05 (ddd, *J* = 12.6 Hz, 4.5 Hz, 0.6 Hz, 1H), 6.85 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 5.52 (br s, 1H), 4.50 (d, *J*= 5.4 Hz)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 157.1, 149.5, 140.6, 137.6, 137.3, 137.0, 123.6, 122.8, 121.6, 118.1, 48.6

FT-IR (NaCl, thin film) ν = 3371, 3063, 1587, 1491, 1435, 1389, 1326, 1055, 996, 789, 757, 729 cm^{-1}.

HRMS (ESI) Calc ($C_{11}H_{11}Cl_1N_3$): 220.0636, Found: 220.0632

R_f (20% EtOAc / Hexanes): 0.20



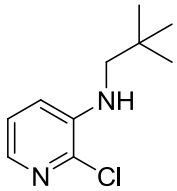
2-Chloro-N-cyclohexylpyridin-3-amine (24g)[50]

Following the general procedure 3-amino-2-chloropyridine (1.0 g, 7.78 mmol), 12 mL EtOAc, cyclohexanone (0.89 mL, 8.56 mmol), trifluoroacetic acid (1.2 mL, 15.6 mmol) and sodium triacetoxyborohydride (1.98 g, 9.34 mmol) were combined and stirred for 30 minutes. The reaction was quenched with 20% $NaOH_{(aq)}$ and the pH was adjusted with $NaOH_{(s)}$ (20 pellets). The layers were separated, the organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give of **24g** as a yellow oil, which was used without further purification (1.73 g, 99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.65 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 7.05 (dd, *J* = 8.1 Hz, 4.5 Hz, 1H), 6.87 (dd, *J* = 8.1 Hz, 1.8 Hz, 1H), 4.25 (br s, 1H), 3.25 (br s, 1H), 2.04-2.00 (m, 2H), 1.82-1.64 (m, 4H), 1.41-1.23 (m, 6H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 140.0, 137.0, 135.8, 123.4, 117.8, 51.3, 32.9, 25.8, 24.8

R_f (20% EtOAc / Hexanes): 0.48



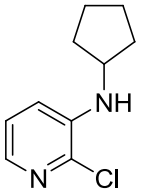
2-Chloro-N-neopentylpyridin-3-amine (24i)[58]

Following the general procedure 3-amino-2-chloropyridine (1.0 g, 7.78 mmol), 12mL EtOAc, pivaldehyde (0.93 mL, 8.56 mmol), trifluoroacetic acid (1.2 mL, 15.6 mmol) and sodium triacetoxyborohydride (1.98 g, 9.34 mmol) were combined and stirred for 30 minutes. The reaction was quenched with 20% $NaOH_{(aq)}$ and the pH was adjusted with $NaOH_{(s)}$ (20 pellets). The layers were separated, the organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give of **24i** as a dark blue oil, which was used without further purification (1.48 g, 95%)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.66 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 7.07 (dd, *J* = 8.1 Hz, 4.5 Hz, 1H), 6.89 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 4.40 (br s, 1H), 2.92 (d, *J* = 5.1 Hz, 2H), 1.02 (s, 9H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 141.5, 136.9, 135.8, 123.5, 117.3, 55.0, 32.2, 27.6

R_f (20% EtOAc / Hexanes): 0.45



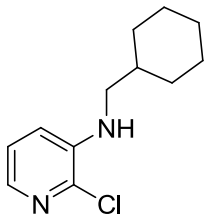
2-Chloro-N-cyclopentylpyridin-3-amine (24j)[50]

Following the general procedure 3-amino-2-chloropyridine (1.29 g, 10.0 mmol), 15mL EtOAc, cyclopentanone(0.97 mL, 11.0 mmol), trifluoroacetic acid (1.54 mL, 20.0 mmol) and sodium triacetoxyborohydride (2.54 g, 12.0 mmol) were combined and stirred for 30 minutes. The reaction was quenched with 20% $NaOH_{(aq)}$ and the pH was adjusted with $NaOH_{(s)}$ (20 pellets). The layers were separated, the organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **24j** as a yellow oil, which was used without further purification (1.61 g, 82%)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.67 (dd, *J* = 4.8 Hz, 1.8 Hz, 1H), 7.07 (ddd, *J* = 8.1 Hz, 4.5 Hz, 0.6 Hz, 1H), 6.90 (dd, *J* = 8.1 Hz, 1.8 Hz, 1H), 4.32 (br s, 1H), 3.76 (sext, 6.3 Hz, 1H), 2.12 – 1.98 (m, 2H), 1.85 – 1.45 (m, 6H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 140.6, 137.0, 135.9, 123.4, 118.1, 54.2, 33.4, 24.1

R_f (20% EtOAc / Hexanes): 0.48



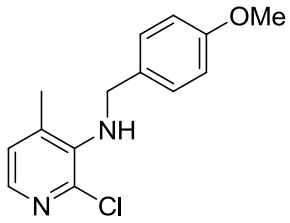
2-Chloro-N-(cyclohexylmethyl)pyridin-3-amine (24k)[50]

Following the general procedure 3-amino-2-chloropyridine (1.29 g, 10.0 mmol), 15mL EtOAc, cyclohexane carboxaldehyde (1.32 mL, 11.0 mmol), trifluoroacetic acid (1.54 mL, 20.0 mmol) and sodium triacetoxyborohydride (2.54 g, 12.0 mmol) were combined and stirred for 30 minutes. The reaction was quenched with 20% $NaOH_{(aq)}$ and the pH was adjusted with $NaOH_{(s)}$ (20 pellets). The layers were separated, the organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give of **24k** as a yellow oil, which was used without further purification (1.95 g, 87%)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.66 (dd, *J* = 4.8 Hz, 1.8 Hz, 1H), 7.06 (dd, *J* = 7.8 Hz, 4.5 Hz, 1H), 6.85 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 4.41 (br s, 1H), 2.98 (t, *J* = 6.3 Hz, 2H) 1.87 – 1.52 (m, 6H), 1.36 – 0.90 (m, 5H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 141.1, 136.9, 135.8, 123.5, 117.3, 49.8, 37.3, 21.2, 26.5, 25.9

R_f (20% EtOAc / Hexanes): 0.49



2-Chloro-N-(4-methoxybenzyl)-4-methylpyridin-3-amine (26)

Following the general procedure 3-amino-2-chloro-4-methylpyridine (2.0 g, 14.03 mmol), 21.6mL EtOAc, 4-methoxybenzaldehyde(1.88 mL, 15.43 mmol), trifluoroacetic acid (2.08 mL, 28.06 mmol) and sodium triacetoxyborohydride (3.57 g, 16.83 mmol) were combined and stirred for 30 minutes. The reaction was quenched with 20% $NaOH_{(aq)}$ and the pH was adjusted with $NaOH_{(s)}$ (20 pellets). The layers were separated, the organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to an oil which was purified on a 5% EtOAc/Hexanes silica gel column to give **26** as a colorless oil (2.98 g, 81%)

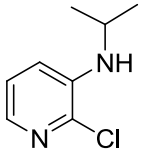
^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.81 (d, *J* = 4.8 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 4.8 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.17 (s, 2H), 3.92 (br s, 1H), 3.76 (s, 3H), 2.33 (s, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 159.0, 143.7, 131.3, 140.8, 139.9, 131.3, 129.0, 125.9, 114.0, 55.2, 51.4, 19.1

FT-IR (NaCl, thin film) ν = 2956, 2917, 2849, 1611, 1586, 1512, 1248, 1174, 1100, 1033, 823 cm^{-1}.

Anal. Calc $C_{14}H_{15}ClN_2O$: C, 64.00; H, 5.75; N, 10.66; found C, 63.61; H, 5.45; N, 10.37

R_f (20% EtOAc / Hexanes): 0.25



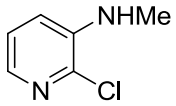
2-Chloro-N-isopropylpyridin-3-amine (24h)[205]

To a flame-dried 5 mL RBF equipped with a stirbar was added 2,2-dimethoxypropane (1.91 mL, 15.6 mmol) followed by 3-amino-2-chloropyridine (1.0 g, 7.78 mmol). The flask was equipped with a reflux condenser and heated to reflux for 6h in a 90°C pre-heated oil bath. The reaction was then concentrated *in vacuo*, dissolved in 25 mL MeOH and sodium borohydride (1.74 g, 45.9 mmol) was added portionwise over 20 minutes. Upon completion of the addition, TLC incidcated consumption of the starting material and the reaction was quenched with 15 mL of water, and extracted with CH_2Cl_2 (4 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give 1.1 g of crude product which was purified on a silica gel column (4.5 cm x 12 cm), eluting with 10% MTBE / Hexanes to give 800 mg (61%) of **24h** as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.67 (dd, *J* = 4.6 Hz, 1.6 Hz, 1H), 7.07 (dd, *J* = 8.1 Hz, 4.6 Hz, 1H), 6.87 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 4.19 (brs, 1H), 3.61 (sept, *J* = 6.2 Hz, 1H), 1.26 (d, *J* = 6.3 Hz, 6H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 140.1, 137.0, 135.9, 123.5, 117.8, 44.0, 22.7

R_f (20% EtOAc / Hexanes): 0.44



2-Chloro-N-methylpyridin-3-amine (24l)[206]

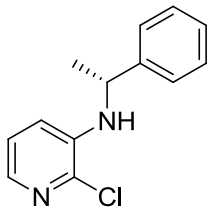
To a flame-dried 25 mL RBF equipped with a stirbar was added *tert*-butyl 2-chloropyridin-3-ylcarbamate[207] (500 mg, 2.19 mmol) and DMF (10 mL). The reaction was cooled to 0°C (ice-water bath) and sodium hydride (60% wt in mineral oil) (66 mg, 2.74 mmol) was added carefully. The reaction mixture was stirred for 10 min, at which time methyl iodide (0.17 mL, 2.74 mmol) was added. The reaction was allowed to warm to RT and stirred for 2 h at which time TLC indicated consumption of the pyridine. The reaction was quenched by the addition of H_2O (5 mL), and diluted with EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 10mL). The combined organic layers were washed with H_2O (3 x 10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give 525 mg of a yellow oil, which was taken on without further purification.

The oil prepared above was dissolved in 7.2 mL CH_2Cl_2 and added to a 25 mL flame-dried RBF equipped with a stirbar. Trifluoroacetic acid (0.35 mL, 4.54 mmol) was added dropwise and the reaction stirred for 3h, at which time TLC indicated consumption of the starting material. The reaction was quenched with 2M $NaOH_{(aq)}$ (10 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 6 mL), the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give 300 mg of a brown oil, which was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.62 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 7.04 (dd, *J* = 8.1 Hz, 4.5 Hz, 1H), 6.78 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 2.81 (s, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 141.8, 137.0, 136.2, 123.6, 116.9, 30.0

(R)-2-Chloro-N-(1-phenylethyl)pyridin-3-amine (24m)



To an oven-dried 100 mL Schlenk-tube equipped with a stirbar was added 3-iodo-2-chloro-pyridine (1.0 g, 4.2 mmol) and toluene (10.5 mL). To this slurry was added palladium (II) acetate (47 mg, 0.21 mmol), *rac*-BINAP (431 mg, 0.21 mmol), cesium carbonate (2.04 g, 6.3 mmol), (*R*)-1-phenylethylamine (0.51 mL, 4.0 mmol), triethylamine (0.06 mL, 0.42 mmol). The reaction mixture was degassed by 2 x vacuum / $Ar_{(g)}$ purge cycles, equipped with a cold-finger, and heated to reflux in a 110 °C pre-heated oil-bath for 36 h. The reaction mixture was then cooled to RT, diluted with H_2O (10 mL), EtOAc (15 mL), and filtered through a Celite plug. The layers were separated, the organic layer dried over $MgSO_4$ and concentrated *in vacuo* to give a grey solid. The crude product was purified on a silica gel column (4.5 cm x 12 cm) eluting with 10% EtOAc / Hexanes to give 650 mg of **24m** as an off-white solid (67%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.65 (dd, *J* = 4.8 Hz, 1.8 Hz, 1H), 7.38 – 7.21 (m, 5H), 6.90 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 6.60 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 4.75 (br s, 1H), 4.48 (pent, *J* = 6.3 Hz, 1H), 1.60 (d, 6.9 Hz, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 143.6, 139.8, 137.0, 136.5, 129.0, 127.4, 125.7, 123.3, 118.9, 53.3, 25.2

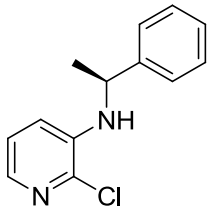
FT-IR (NaCl, thin film) ν = 3420, 3061, 3028, 2979, 1583, 1561, 1488, 1451, 1383, 1328, 1311, 1055, 788, 701 cm^{-1}.

HRMS (ESI) Calc $(C_{13}H_{13}ClN_2)H^+$: 233.0840, Found: 233.0845

MP: 68 - 70 °C

$[\alpha]_D$ = -102° (c = 1.0, MeOH)

R_f (20% EtOAc / Hexanes): 0.40



(*S*)-2-Chloro-N-(1-phenylethyl)pyridin-3-amine (24n)

To an oven-dried 100 mL Schlenk-tube equipped with a stirbar was added 3-iodo-2-chloro-pyridine[58] (1.0 g, 4.2 mmol) and toluene (10.5 mL). To this slurry was added sequentially palladium (II) acetate (47 mg, 0.21 mmol), *rac*-BINAP (431 mg, 0.21 mmol), cesium carbonate (2.04 g, 6.3 mmol), and (*S*)-1-phenylethylamine (0.51 mL, 4.0 mmol), triethylamine (0.06 mL, 0.42 mmol). The reaction mixture was degassed by 2x vacuum / $Ar_{(g)}$ purge cycles. The Schlenk flask was equipped with a cold-finger condenser under a positive pressure of argon gas and heated to reflux in a 110 °C pre-heated oil-bath for 36 h, cooled to RT, diluted with H_2O (10 mL) and EtOAc (15 mL), the mixture was then filtered through a Celite plug. The layers were separated, the organic layer dried over $MgSO_4$ and concentrated *in vacuo* to give a grey solid. The crude product was purified on a silica gel column (4.5 cm x 12 cm) eluting with 10% EtOAc / Hexanes to give 620 mg of **24n** as a white solid (64%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.65 (dd, *J* = 4.8 Hz, 1.8 Hz, 1H), 7.38 – 7.21 (m, 5H), 6.90 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 6.61 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 4.76 (br s, 1H), 4.48 (br q, *J* = 6.3 Hz, 1H), 1.60 (d, 6.9 Hz, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 143.9, 140.2, 137.2, 136.8, 129.3, 127.8, 126.0, 123.7, 119.3, 53.7, 25.5

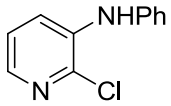
FT-IR (NaCl, thin film) ν = 3420, 3061, 3028, 2979, 1583, 1561, 1488, 1451, 1383, 1328, 1311, 1055, 788, 701 cm^{-1}.

HRMS (ESI) Calc $(C_{13}H_{12}N_2Cl)H^+$: 233.0840, Found: 233.0846

MP: 69 - 70 °C

$[\alpha]_D$ = +102° (c = 1.0, MeOH)

R_f (20% EtOAc / Hexanes): 0.40



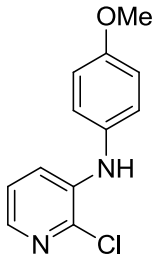
2-Chloro-N-phenylpyridin-3-amine (24o)[58]

To a flame-dried 100 mL RBF equipped with a stirbar was added activated 4Å mol. Sieves (2 g), phenylboronic acid (1.9 g, 15.56 mmol), 3-amino-2-chloropyridine (1.0 g, 7.78 mmol), $Cu(OAc)_2$ (2.12 g, 11.67 mmol), pyridine (1.23 mL, 15.5 mmol) and CH_2Cl_2 (39 mL). The flask was equipped with a balloon of $O_{2(g)}$ and stirred for 4d at which time TLC showed consumption of the pyridine. The reaction was quenched with $NH_4OH_{(aq)}$ (15 mL) causing a color change to dark blue from brown. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated to give a brown oil. The oil was purified on a silica gel column (4.5 cm x 12 cm), eluting with 10% EtOAc / hexanes to give 1.34 g of a white crystalline solid (84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.87 (dd, *J* = 4.8 Hz, 1.8 Hz, 1H), 7.49 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.40 – 7.33 (m, 2H), 7.20 – 7.13 (m, 2H), 7.13 – 7.05 (m, 2H), 6.14 (br s, 1H)

MP: 72 – 76 °C

R_f (20% EtOAc / Hexanes): 0.36



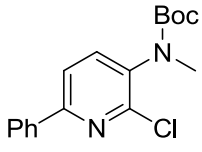
2-Chloro-N-(4-methoxyphenyl)pyridin-3-amine (24p)[28]

To a flame-dried 100 mL RBF equipped with a stirbar was added 5g of activated 4Å mol. sieves, *p*-methoxyphenylboronic acid (2.36 g, 15.56 mmol) followed by 3-amino-2-chloropyridine (1.0 g, 7.78 mmol), $Cu(OAc)_2$ (2.12 g, 11.67 mmol), pyridine (1.23 mL, 15.56 mmol) and CH_2Cl_2 (39 mL). The reaction was stirred for 6 d at RT under a balloon of $O_{2(g)}$. The reaction was quenched with $NH_4OH_{(aq)}$(15 mL); the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated to give a purple oil which was purified on a silica gel column (4.5 cm x 12 cm), eluting with 20% EtOAc / hexanes to give 650 mg of a white crystalline solid (36%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.77 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 7.16 (dd *J* = 8.1 Hz, 1.8 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 2H), 7.00 (dd, *J* = 8.1 Hz, 4.5 Hz, 1H), 6.89 (d, *J* = 9 Hz), 5.99 (br s, 1H), 3.81 (s, 3H)

MP = 62 – 63 °C

R_f (20% EtOAc / Hexanes): 0.28



tert-Butyl 2-chloro-6-phenylpyridin-3-yl(methyl)carbamate (SI2)

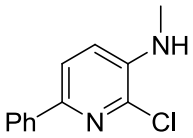
To an oven-dried 100 mL RBF equipped with a stirbar was added KHMDS (5.29 g, 26.5 mmol) and 26.5 mL THF. The reaction was stirred until dissolution (0.5 h), cooled to 0°C (ice-water bath). 6-Bromo-2-chloropyridin-3-amine[205] (2.5 g, 12.05 mmol) was added as a 1M solution in THF (12 mL), the reaction mixture was stirred for 10 min at which time di-*tert*-butyl dicarbonate (2.76 g, 12.65 mmol) was added as a solid. The reaction mixture was stirred for 0.5 h at which time iodomethane (0.83 mL, 13.26 mmol) was added via syringe. The reaction was warmed to RT, stirred for 10 h, quenched with 20 mL water, and diluted with 20 mL EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 2.1 g of *tert*-butyl 6-bromo-2-chloropyridin-3-yl(methyl)carbamate (**SI1**) a white solid (54%).

To a flame-dried 50 mL RBF equipped with a stirbar was added pyridine **SI1** (1.0 g, 3.1 mmol), 1,4-dioxane (15.5 mL), phenylboronic acid (397 mg, 3.3 mmol) and potassium carbonate (1.33 g, 9.61 mmol). The reaction mixture was degassed by 3x vacuum / $Ar_{(g)}$ purge cycles, tetrakis(triphenylphosphine)palladium (179 mg, 0.16 mmol) added, and the reaction mixture placed in an 80°C pre-heated oil-bath. The reaction mixture was then stirred for 48 h, cooled to RT, diluted with EtOAc (15 ml), washed with water (10 mL), brine (5 mL), dried over $MgSO_4$, concentrated *in vacuo* to give a dark brown solid which was purified on a silica gel column, eluting with 10% EtOAc / Hexanes to give 460 mg of a pale yellow solid (47%).

^{1}H NMR (300 MHz, $CDCl_3$) δ=8.10 – 7.90 (m, 2H), 7.75 – 7.60 (m 2H), 7.55 – 7.30 (m, 3H), 3.19 (s, 2.7 H, rotomer), 3.14 (s, 0.3H, rotomer), 1.60 – 1.20 (2 x brs, rotomers, 9H)
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 156.0, 154.4, 149.8, 138.4, 137.2, 136.3, 129.8, 129.0, 127.1, 119.4, 81.1, 36.3, 28.3

FT-IR (NaCl, thin film) ν = 2917, 1708, 1533, 1458, 1438, 1366, 1318, 1153, 1064, 748 cm^{-1}.

Anal. Calc $C_{17}H_{19}ClN_2O_2$: C, 64.05; H, 6.01; N, 8.79; found C, 64.04; H, 5.63; N, 8.48



2-Chloro-N-methyl-6-phenylpyridin-3-amine (27)

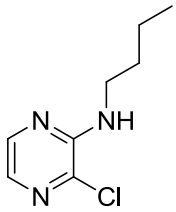
To a flame-dried 25 mL RBF equipped with a stirbar was added **SI2** (450 mg, 1.41 mmol) followed by 4.7 mL CH_2Cl_2. Trifluoroacetic acid (0.23 mL, 2.96 mmol) was added dropwise and the reaction mixture stirred at RT for 24h. The reaction mixture was quenched with 1N $NaOH_{(aq)}$(10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL), combined organic layers dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified on a silica gel column, eluting with 20% EtOAc / Hexanes to give 290 mg of a pale brown crystalline solid (94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.93 – 7.80 (m, 2H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.35 – 7.28 (m, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 2.96 (s, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 144.8, 140.6, 138.3, 136.7, 128.7, 127.9, 125.9, 120.1, 117.7, 30.1

FT-IR (NaCl, thin film) ν = 2915, 2886, 1592, 1491, 1055 cm^{-1}.

Anal. Calc $C_{12}H_{11}ClN_2$: C, 65.91; H, 5.07; N, 12.81; found C, 65.83; H, 5.24; N, 12.93



N-Butyl-3-chloropyrazin-2-amine (28)

To a flame-dried 25 mL RBF equipped with a stirbar was added 2,3-dichloropyrazine (5.0 g, 33.6 mmol), 1,4-dioxane (8 mL), *n*-butylamine (4.0 mL, 40.3 mmol) and triethylamine (7.02 mL, 50.3 mmol). The reaction vessel was equipped with a condenser, and heated to 100°C in a pre-heated oil-bath for 8 h. The reaction was cooled to RT, concentrated, diltuted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, decanted, and concentrated *in vacuo* to give **28** as a yellow oil, which was used without further purification (6.1 g, 98%).

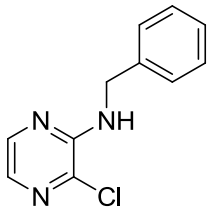
^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.93 (d, *J* = 2.7 Hz, 1H), 7.54 (d, *J* = 2.7 Hz, 1H), 5.18 (br s, 1H), 3.45 (td, *J* = 6.9 Hz, 5.7 Hz, 2H), 1.64 (pent, *J* = 6.9 Hz, 2H), 1.43 (sex, *J* = 7.5 Hz, 2H), 0.97 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 151.2, 140.7, 134.7, 130.3, 41.2, 31.5, 20.2, 13.9

FT-IR (NaCl, thin film) ν = 3439, 3351, 2958, 2872, 1582, 1520, 1465, 1436, 1350, 1238, 1169, 1046, 827 cm^{-1}.

HRMS (ESI+) Calc $(C_{18}H_{12}ClN_3)H^+$: 186.0793, Found: 186.0801

R_f (20% EtOAc / Hexanes): 0.51



N-Benzyl-3-chloropyrazin-2-amine (29)

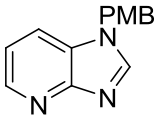
To a flame-dried 25 mL RBF equipped with a stirbar was added 2,3-dichloropyrazine (5.0 g, 33.6 mmol), 8 mL 1,4-dioxane, benzyl amine (4.4 mL, 40.3 mmol) and triethylamine (7.02 mL, 50.3 mmol). The reaction vessel was equipped with a condenser, and heated to 100°C in a pre-heated oil-bath for 8h. The reaction mixture was cooled to RT, concentrated, diltuted with H_2O (15 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give **29** as a yellow crystalline sold, which was used without further purification (5.3 g, 72%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.97 (d, 3 Hz, 1H), 7.61 (d, *J* = 2.7 Hz, 1H), 7.40 – 7.27 (m, 5H), 5.50 (br s, 1H), 4.67 (d, *J* = 5.7 Hz, 2H)

MP: 53 – 55 °C

R_f (20% EtOAc / Hexanes): 0.40

Palladium-Catalyzed Amidation/Cyclization Representative Procedure:



1-(4-Methoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (25a)

To an oven-dried 25 mL Schlenk-tube equipped with a stirbar was added $Pd_2(dba)_3 \cdot CHCl_3$ (20.8 mg, 0.02 mmol), 2-di-t-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-tri-i-propylbiphenyl (**L1**) (48 mg, 0.1 mmol), K_3PO_4 (639 mg, 3.01 mmol) and 2-chloro-N-(4-methoxybenzyl)pyridin-3-amine (**24a**) (500 mg, 2.01 mmol) (if solid). The tube was evacuated and refilled with $Ar_{(g)}$. Formamide (0.12 mL, 3.01 mmol) was added via syringe as a single portion, followed by the chloropyridine (if liquid) in 4 mL of *tert*-butanol. The reaction mixture was degassed with 3 x vacuum / $Ar_{(g)}$ purge cycles. The reaction vessel was then equipped with a cold-finger condensor under a positive pressure of argon gas and immersed in a 110°C pre-heated oil-bath for 4h at which time TLC indicated consumption of the chloro-pyridine. The reaction was cooled to room temperature, diluted with MeOH (4 mL) filtered through a Celite plug and concentrated *in vacuo* to give a dark brown oil. The crude product was purified on a silica gel column (4.5 cm x 12 cm), eluting with 4% MeOH in CH_2Cl_2 to give 408 mg of a brown crystalline solid (85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.56 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 8.16 (s, 1H), 7.58 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.20 – 7.15 (m, 3H), 6.88 (d, 8.7 Hz, 2H), 5.30 (s, 2H), 3.80 (s, 3H)

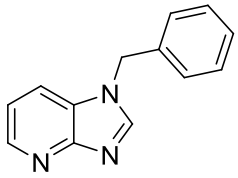
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 159.5, 156.3, 145.1, 144.7, 128.6, 126.5, 126.0, 118.4, 117.9, 114.3, 55.2, 48.9

FT-IR (NaCl, thin film) ν = 3361, 3071, 2932, 2835, 1610, 1513, 1493, 1288, 1253, 1033 cm^{-1}.

HRMS (ESI+) Calc ($C_{14}H_{14}N_3O$) (M + H): 240.1131, Found: 240.1132

MP: 120 - 122 °C

R_f (4% MeOH / CH_2Cl_2): 0.23



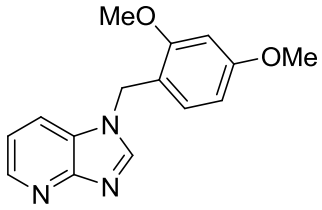
1-Benzyl-1H-imidazo[4,5-*b*]pyridine (25b)[41]

Following the general experimental; N-benzyl-2-chloropyridin-3-amine (**24b**) (87.5 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.14 mg, 0.004 mmol), *t*-BuBrettPhos (9.7 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), formamide (0.024 mL, 0.6 mmol) were combined with 2 mL *tert*-butanol in a 25 mL Schlenk flask. After 4h TLC analysis indicated the reaction was complete. The reaction was cooled to RT, filtered through Celite, concentrated and purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give **25b** as 75 mg of a yellow solid (90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.50 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 8.14 (s, 1H), 7.53 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.34 – 7.24 (m, 3H), 7.18 – 7.08 (m, 3H), 5.34 (s, 2H)

MP: 118 – 120 °C

R_f (4% MeOH / CH_2Cl_2): 0.24



1-(2,4-Dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (25c)

Following the general experimental; 2-chloro-N-(2,4-dimethoxybenzyl)pyridin-3-amine (**24c**) (2.5 g, 8.97 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (93 mg, 0.09 mmol), **L1** (215 mg, 0.45 mmol), K_3PO_4 (2.86 g, 13.45 mmol), formamide (0.53 mL, 13.45 mmol) were combined with 45 mL *tert*-butanol in a 100 mL Schlenk flask. After 5h the reaction was complete as indicated by TLC analysis. The reaction mixture was cooled to RT, diluted with MeOH (20 mL), filtered through Celite, concentrated *in vacuo* and purified on a silica gel column(4.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give **25c** as 1.96 g of a dark yellow solid (82%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.47 (dd, *J*= 4.8 Hz, 1.5 Hz, 1H), 8.13 (s, 1H), 7.68 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.11 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 7.06 (d, *J* = 8.7 Hz, 1H), 6.42 – 6.37 (m, 2H), 5.21 (s, 2H), 3.75 (s, 6H)

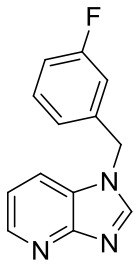
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 161.5, 158.5, 156.4, 145.8, 144.6, 130.5, 126.3, 118.3, 117.9, 115.4, 104.4, 98.9, 55.5, 55.4, 44.7

FT-IR (NaCl, thin film) ν = 2917, 2848, 1613, 1589, 1509, 1414, 1289, 1209, 1158, 1033 cm^{-1}.

HRMS (ESI+) Calc ($C_{15}H_{16}N_3O_2$) (M + H): 270.1237, Found: 240.1136

MP: 131 – 134 °C

R_f (4% MeOH / CH_2Cl_2): 0.22



1-(3-Fluorobenzyl)-1H-imidazo[4,5-*b*]pyridine (25d)

Following the general experimental; 2-chloro-N-(3-fluorobenzyl)pyridin-3-amine (**24d**) (95 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.14 mg, 0.004 mmol), *t*-BuBrettphos (9.7 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), formamide (0.022 mL, 0.6 mmol) were combined with 2.0 mL *tert*-butanol in a 25 mL Schlenk flask. After 4 h the reaction was complete, the reaction cooled to RT, filtered through Celite, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give **25d** as 82 mg of a green solid (90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.52 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 8.17 (s, 1H), 7.53 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.28 (td, *J* = 7.8 Hz, 6 Hz, 1H), 7.13 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 7.01 – 6.95 (m, 1H), 6.93 – 6.90 (m, 1H), 6.85 – 6.81 (m, 1H), 5.36 (s, 2H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 163.1 (d, J_{C-F} = 247 Hz), 156.4, 145.4, 145.2, 137.3 (d, J_{C-F} = 7 Hz), 130.9 (d, J_{C-F} = 8 Hz), 126.1, 122.7 (d, J_{C-F} = 3 Hz), 118.4, 118.4, 115.6 (d, J_{C-F} = 20 Hz), 114.2 (d, J_{C-F} = 20 Hz), 48.9 (d, J_{C-F} = 1.7 Hz)

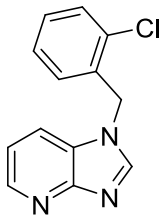
^{19}F NMR (282.4 MHz, $CDCl_3$) δ= -111.79 (td, *J* = 8.5 Hz, 5.6 Hz)

FT-IR (NaCl, thin film) ν = 1612, 1592, 1492, 1452, 1415, 1377, 1261, 1293, 1252, 780 cm^{-1}.

HRMS (ESI) Calc ($C_{13}H_{11}N_3F_1$): 228.0932, Found: 228.0929

MP: 117 - 121°C

R_f (4% MeOH / CH_2Cl_2): 0.23



1-(2-Chlorobenzyl)-1H-imidazo[4,5-*b*]pyridine (25e)

Following the general experimental; 2-chloro-N-(2-chlorobenzyl)pyridin-3-amine (**24e**) (101 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.14 mg, 0.004 mmol), *t*-BuBrettphos (9.7 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), formamide (0.022 mL, 0.6 mmol) were combined with 2.0 mL *tert*-butanol in a 25 mL Schlenk flask. After 4 h the reaction was complete, the reaction cooled to RT, filtered through Celite, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give **25e** as 50 mg of a green solid (51%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.61 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 8.26 (s, 1H), 7.70 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.49 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.34 (td, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.29 – 7.21 (m, 2H), 7.01 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 5.53 (s, 2H)

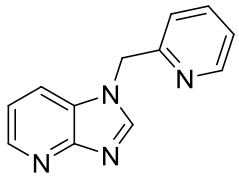
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 156.3, 145.7, 145.3, 133.4, 132.4, 130.3, 130.2, 129.0, 127.6, 126.2, 118.4, 118.4, 47.1

FT-IR (NaCl, thin film) ν = 3391, 2963, 2923, 1642, 1611, 1494, 1444, 1416, 1378, 1262, 1295, 1212, 780 cm^{-1}.

HRMS (ESI) Calc ($C_{13}H_{11}N_3Cl_1$): 244.0636, Found: 244.0643

MP: 135 – 137 °C

R_f (4% MeOH / CH_2Cl_2): 0.24



1-(Pyridin-2-ylmethyl)-1H-imidazo[4,5-*b*]pyridine (25f)

Following the general experimental; 2-chloro-N-(pyridin-2-ylmethyl)pyridin-3-amine (**24f**) (93 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.14 mg, 0.004 mmol), **L1** (9.6 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), formamide (0.022 mL, 0.6 mmol) were combined with 2.0 mL *tert*-butanol in a 25 mL Schlenk flask. After 4 h the reaction was complete, the reaction cooled to RT, filtered through Celite, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give **25f** as 81 mg of a brown solid (95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.60 (ddd, *J* = 4.8 Hz, 1.5 Hz, 0.9 Hz, 1H), 8.57 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 8.31 (s, 1H), 7.70 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.65 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.20 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 1H), 5.50 (s, 2H)

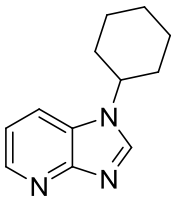
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 156.4, 154.8, 150.1, 145.7, 145.3, 145.2, 137.6, 123.5, 121.5, 118.7, 118.5, 51.3

FT-IR (NaCl, thin film) ν = 3391, 1647, 1614, 1495, 1419, 1439, 1379, 1363, 1292, 783 cm^{-1}.

HRMS (ESI) Calc ($C_{12}H_{10}N_4$): 210.0905, Found: 210.0905

MP: 165 – 169 °C

R_f (4% MeOH / CH_2Cl_2): 0.20



1-Cyclohexyl-1H-imidazo[4,5-*b*]pyridine (25g)

Following the general experimental; 2-chloro-N-cyclohexylpyridin-3-amine (**24g**) (84.3 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.14 mg, 0.004 mmol), t-BuBrettPhos (9.7 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), formamide (0.024 mL, 0.6 mmol) were combined with 2 mL *tert*-butanol in a 25 mL Schlenk flask. After 4h the reaction was complete, the reaction cooled to RT, filtered through Celite, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give **25g** as 69 mg of a white solid (90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.54 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 8.18 (s, 1H), 7.75 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.18 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 4.18 (tt, *J* = 12 Hz, 3.9 Hz, 1H), 2.24 – 2.13 (m, 2H), 2.02 – 1.92 (m, 2H), 1.88 – 1.72 (m, 3H), 1.49 (qt, *J* = 12.9 Hz, 3.3 Hz, 2H), 1.30 (qt, *J* = 12.6 Hz, 3.0 Hz, 1H)

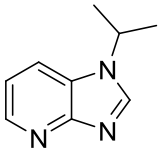
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 156.6, 145.0, 142.8, 125.6, 118.4, 117.8, 56.2, 33.3, 25.7, 25.4

FT-IR (NaCl, thin film) ν = 2935, 2858, 1607, 1486, 1414, 1281, 1219, 786 cm^{-1}.

HRMS (ESI) Calc ($C_{12}H_{15}N_3$): 201.1265, Found: 201.1266

MP: 151 – 153 °C

R_f (4% MeOH / CH_2Cl_2): 0.25



1-Isopropyl-1H-imidazo[4,5-*b*]pyridine (25h)

Following the general experimental; 2-chloro-N-isopropylpyridin-3-amine (**24h**) (68 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.14 mg, 0.004 mmol), *t*-BuBrettphos (9.7 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), formamide (0.022 mL, 0.6 mmol) were combined with 2.0 mL *tert*-butanol in a 25 mL Schlenk flask. After 3 h the reaction was complete, the reaction cooled to RT, filtered through Celite, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give **25h** as 59 mg of a white solid (91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.53 (dd, *J* = 4.5 Hz, 1.2 Hz, 1H), 8.19 (s, 1H), 7.75 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.20 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 4.63 (sept, *J* = 6.6 Hz, 1H), 1.61 (d, *J* = 6.6 Hz, 6H)

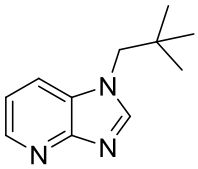
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 156.4, 144.9, 142.6, 125.5, 118.5, 117.9, 48.6, 22.6

FT-IR (NaCl, thin film) ν = 2980, 2936, 1607, 1488, 1397, 1306, 1282, 1225, 786 cm^{-1}.

HRMS (ESI) Calc $(C_9H_{11}N_3)H^+$: 162.1026, Found: 162.1033

MP: 134 – 136 °C

R_f (4% MeOH / CH_2Cl_2): 0.25



1-Neopentyl-1H-imidazo[4,5-*b*]pyridine (25i)

Following the general experimental; 2-chloro-N-neopentylpyridin-3-amine (**24i**) (71.3 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.14 mg, 0.004 mmol), *t*-BuBrettphos (9.7 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), formamide (0.022 mL, 0.6 mmol) were combined with 2.0 mL *tert*-butanol in a 25 mL Schlenk flask. After 3 h the reaction was complete, the reaction cooled to RT, filtered through Celite, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give **25i** as 57 mg of a white solid (75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.55 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 8.07 (s, 1H), 7.72 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.22 (dd, *J* = 8.1 Hz, 4.5 Hz, 1H), 3.94 (s, 2H), 1.02 (s, 9H)

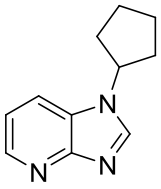
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 155.9, 146.4, 144.8, 127.3, 118.6, 118.2, 57.2, 33.9, 27.9

FT-IR (NaCl, thin film) ν = 3466, 2956, 2873, 1641, 1495, 1416, 1400, 1383, 1364, 1297 cm^{-1}.

HRMS (ESI) Calc $(C_{11}H_{15}N_3)H^+$: 190.1339, Found: 190.1347

MP: 139 – 142 °C

R_f (4% MeOH / CH_2Cl_2): 0.24



1-Cyclopentyl-1H-imidazo[4,5-*b*]pyridine (25j)

Following the general experimental; 2-chloro-N-cyclopentylpyridin-3-amine (**24j**) (78.7 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.14 mg, 0.004 mmol), t-BuBrettPhos (9.7 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), formamide (0.024 mL, 0.6 mmol) were combined with 2 mL *tert*-butanol in a 25 mL Schlenk flask. After 4h the reaction was complete, the reaction cooled to RT, filtered through Celite, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give **25j** as 64 mg of a white solid (85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.54 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 8.16 (s, 1H), 7.75 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.19 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 4.73 (pent, *J* = 13.8 Hz, 1H), 2.36 – 2.22 (m, 2H), 2.08 – 1.73 (m, 6H)

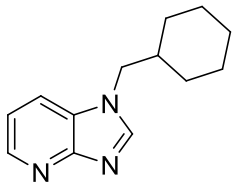
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 156.8, 145.0, 143.2, 126.0, 118.6, 117.8, 57.6, 32.3, 24.0

FT-IR (NaCl, thin film) ν = 2959, 2873, 1605, 1477, 1412, 1291, 1226, 782 cm^{-1}.

HRMS (ESI) Calc ($C_{11}H_{13}N_3$): 187.1109, Found: 187.1109

MP: 90 – 94 °C

R_f (4% MeOH / CH_2Cl_2): 0.25



1-(Cyclohexylmethyl)-1H-imidazo[4,5-*b*]pyridine (25k)

Following the general experimental; 2-chloro-N-(cyclohexylmethyl)pyridin-3-amine (**24k**) (89.9 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.14 mg, 0.004 mmol), *t*-BuBrettPhos (9.7 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), formamide (0.024 mL, 0.6 mmol) were combined with 2 mL *tert*-butanol in a 25 mL Schlenk flask. After 4h the reaction was complete, the reaction cooled to RT, filtered through Celite, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give **25k** as 72.3 mg of a white solid (84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.50 (dd, *J* = 4.8 Hz, 1.8 Hz, 1H), 8.01 (s, 1H), 7.67 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.17 (dd *J* = 8.1 Hz, 4.8 Hz, 1H), 3.95 (d, *J* = 7.2 Hz, 2H), 1.86 – 1.51 (m, 6H), 1.21 – 0.86 (m, 5H)

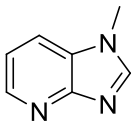
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 156.3, 145.6, 144.8, 126.5, 118.1, 118.0, 51.9, 38.5, 30.8, 26.0, 25.5

FT-IR (NaCl, thin film) ν = 3100, 3050, 2928, 2848, 1610, 1493, 1447, 1414, 1383, 1286, 1205, 1145, 786 cm^{-1}.

HRMS (ESI) Calc ($C_{13}H_{17}N_3$): 215.1421, Found: 215.1422

MP: 105 – 108 °C

R_f (4% MeOH / CH_2Cl_2): 0.26

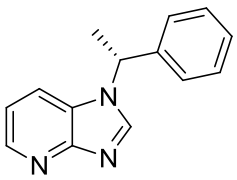


1-Methyl-1H-imidazo[4,5-*b*]pyridine (25l)[208]

Following the general experimental; 2-chloro-N-methylpyridin-3-amine (**24l**) (57 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.14 mg, 0.004 mmol), **L1** (9.6 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), formamide (0.022 mL, 0.6 mmol) were combined with 2.0 mL *tert*-butanol in a 25 mL Schlenk flask. After 4 h the reaction was complete, the reaction cooled to RT, filtered through Celite, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give **25l** as 47 mg of a brown solid (89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.52 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 8.03 (s, 1H), 7.68 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.19 (dd, *J* = 7.8 Hz, 4.5 Hz, 1H), 3.83 (s, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 156.2, 145.7, 144.9, 126.8, 118.1, 117.7, 31.5



(*R*)-1-(1-Phenylethyl)-1H-imidazo[4,5-*b*]pyridine (25m)

Following the general experimental; (*R*)-2-chloro-N-(1-phenylethyl)pyridin-3-amine (**24m**) (93 mg, 0.4 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (4.14 mg, 0.004 mmol), *t*-BuBrettphos (9.7 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), formamide (0.022 mL, 0.6 mmol) were combined with 2.0 mL *tert*-butanol in a 25 mL Schlenk flask. After 4 h the reaction was complete, the reaction cooled to RT, filtered through Celite, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give **25m** as 70 mg of a pale yellow solid (77%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.52 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 8.32 (s, 1H), 7.44 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.19 – 7.14 (m, 2H), 7.09 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 5.62 (q, *J* = 7.2 Hz, 1H), 2.01 (d, *J* = 6.9 Hz, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 156.6, 145.2, 143.3, 140.0, 129.3, 128.6, 126.0, 125.9, 119.2, 118.1, 56.0, 21.5

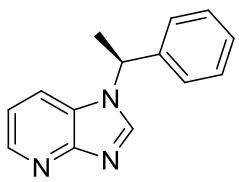
FT-IR (NaCl, thin film) ν = 3402, 2959, 2982, 1606, 1486, 1455, 1414, 1390, 1280, 1230, 1025, 783 cm^{-1}.

HRMS (ESI) Calc $(C_{14}H_{13}N_3)H^+$: 224.1182, Found: 224.1188

MP: 119 - 121°C

$[\alpha]_D$ = + 25° (0.08, MeOH)

R_f (4% MeOH / CH_2Cl_2): 0.23



(S)-1-(1-Phenylethyl)-1H-imidazo[4,5-*b*]pyridine (25n)

Following the general experimental; (*S*)-2-chloro-N-(1-phenylethyl)pyridin-3-amine (**24n**) (93 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.14 mg, 0.004 mmol), *t*-BuBrettphos (9.7 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), formamide (0.022 mL, 0.6 mmol) were combined with 2.0 mL *tert*-butanol in a 25 mL Schlenk flask. After 4 h the reaction was complete, the reaction cooled to RT, filtered through Celite, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give **25n** as 71 mg of a green solid (79%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.46 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 8.26 (s, 1H), 7.39 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.32 – 7.20 (m, 3H), 7.15 – 7.08 (m, 2H), 7.02 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 5.57 (q, *J* = 6.9 Hz, 1H), 1.95 (d, *J* = 6.9 Hz, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 156.6, 145.1, 143.2, 140.0, 129.2, 128.4, 126.0, 125.9, 119.1, 118.0, 56.0, 21.4

FT-IR (NaCl, thin film) ν = 3375, 3085, 2983, 1607, 1487, 1455, 1415, 1290, 1281, 1281, 1230, 783 cm^{-1}.

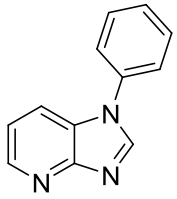
HRMS (ESI) Calc $(C_{14}H_{13}N_3)H^+$: 224.1182, Found: 224.1188

MP: 119 - 121°C

$[\alpha]_D$ = - 50° (0.24, MeOH)

R_f (4% MeOH / CH_2Cl_2): 0.23

1-Phenyl-1H-imidazo[4,5-*b*]pyridine (25o)



Following the general experimental; 2-chloro-N-(phenyl)pyridin-3-amine (**24o**) (82 mg, 0.36 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.14 mg, 0.004 mmol), **L1** (9.6 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), formamide (0.022 mL, 0.6 mmol) were combined with 2 mL *tert*-butanol in a 25 mL Schlenk flask. After 4 h the reaction was complete, the reaction cooled to RT, filtered through Celite, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give **25o** as 76.5 mg of a white solid (98%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.65 (d, *J* = 4.5 Hz, 1H), 8.37 (s, 1H), 7.89 (dd, *J* = 8.1 Hz, 1.2 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.55 – 7.47 (m, 3H), 7.30 (dd, *J* = 8.4 Hz, 4.8 Hz, 1H)

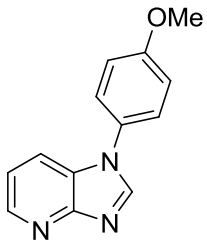
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 145.6, 145.6, 144.5, 135.8, 130.5, 128.8, 126.3, 124.0, 119.1, 119.0

FT-IR (NaCl, thin film) ν = 3124, 1597, 1502, 1477, 1412, 1301, 1194, 785 cm^{-1}.

HRMS (ESI) Calc ($C_{12}H_9N_3$): 195.0796, Found: 195.0794

MP: 120 – 124 °C

R_f (4% MeOH / CH_2Cl_2): 0.24



1-(4-Methoxyphenyl)-1H-imidazo[4,5-*b*]pyridine (25p)

Following the general experimental; 2-chloro-N-(4-methoxyphenyl)pyridin-3-amine (**24p**) (85 mg, 0.36 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.14 mg, 0.004 mmol), *t*-BuBrettPhos (9.7 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), formamide (0.022 mL, 0.6 mmol) were combined with 1.8 mL *tert*-butanol in a 25 mL Schlenk flask. After 3 h the reaction was complete, the reaction cooled to RT, filtered through Celite, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give **25p** as 74 mg of a white solid (91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.54 (dd, *J* = 4.8 Hz, 1.8 Hz, 1H), 8.23 (s, 1H), 7.73 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.35 (dd, *J* = 9 Hz, 2.4 Hz, 2H), 7.20 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 7.05 (dd, *J* = 9 Hz, 2.1 Hz, 2H), 3.85 (s, 3H)

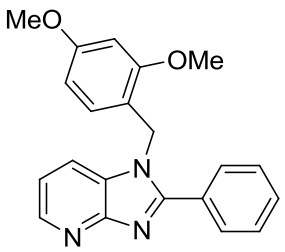
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 159.7, 156.3, 145.4, 144.5, 129.4, 126.6, 125.5, 118.7, 118.6, 115.4, 55.7

FT-IR (NaCl, thin film) ν = 3401, 3080, 2963, 2839, 1609, 1517, 1489, 1415, 1252, 1030, 975, 836 cm^{-1}.

HRMS (ESI) Calc ($C_{13}H_{12}O_1N_3$): 226.0975, Found: 226.0971

MP: 125 – 129 °C

R_f (4% MeOH / CH_2Cl_2): 0.24



1-(2,4-Dimethoxybenzyl)-2-phenyl-1H-imidazo[4,5-*b*]pyridine (30)

Following the general experimental; 2-chloro-N-(2,4-dimethoxybenzyl)pyridin-3-amine (**24c**) (111.5 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.14 mg, 0.004 mmol), *t*-BuBrettphos (9.7 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), benzamide (73 mg, 0.6 mmol) were combined with 2.0 mL *tert*-butanol in a 25 mL Schlenk flask. After 24 h no further progress was observed by TLC, the reaction was cooled to RT, filtered through Celite, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 3% MeOH / CH_2Cl_2 to give **30** as 89 mg of a green semi-solid (65%).

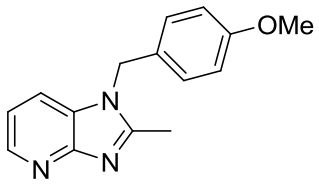
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.54 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 7.86-7.74 (m, 2H), 7.53-7.36 (m, 4H), 7.11 (dd, *J* = 7.8 Hz, 4.8 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.32 (dd, *J* = 8.4 Hz, 2.4 Hz), 5.38 (s, 2H), 3.76 (s, 6H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 160.9, 157.6, 156.5, 155.9, 145.2, 131.9, 130.3, 129.8, 129.5, 128.8, 128.6, 127.8, 127.6, 118.9, 118.0, 116.2, 104.2, 98.8, 53.5, 44.2

FT-IR (NaCl, thin film) ν = 3000, 2937, 2838, 1674, 1612, 1589, 1508, 1468, 1412, 1386, 1209, 1032 cm^{-1}.

HRMS (ESI) Calc ($C_{21}H_{20}N_3O_2$): 346.1550, Found: 346.1545

R_f (4% MeOH / CH_2Cl_2): 0.29



1-(4-Methoxybenzyl)-2-methyl-1H-imidazo[4,5-*b*]pyridine (31)

Following the general experimental; 2-chloro-N-(4-methoxybenzyl)pyridin-3-amine (**24a**) (111.5 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.14 mg, 0.004 mmol), *t*-BuBrettphos (9.7 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), acetamide (35 mg, 0.6 mmol) were combined with 2.0 mL *tert*-butanol in a 25 mL Schlenk flask. After 24 h no further progress was observed by TLC. The reaction was cooled to RT, filtered through Celite, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 3% MeOH / CH_2Cl_2 to give **31** as 61 mg of a green solid (60%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.45 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H), 7.46 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.07 (dd, *J* = 7.8 Hz, 4.8 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.23 (s, 2H), 3.75 (s, 3H), 2.60 (s, 3H)

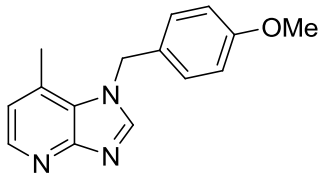
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 159.5, 155.6, 154.7, 144.4, 127.7, 127.7, 127.2, 117.5, 117.3, 114.5, 55.4, 47.0, 14.4

FT-IR (NaCl, thin film) ν = 3249, 2936, 2839, 1612, 1513, 1415, 1252, 1178, 782 cm^{-1}.

HRMS (ESI) Calc $(C_{15}H_{15}N_3O)Na^+$: 276.1107, Found: 276.1103

MP: 110 – 112 °C

R_f (4% MeOH / CH_2Cl_2): 0.26



1-(4-Methoxybenzyl)-7-methyl-1H-imidazo[4,5-*b*]pyridine (32)

Following the general experimental; 2-chloro-N-(4-methoxybenzyl)-4-methylpyridin-3-amine (**26**) (93 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.14 mg, 0.004 mmol), **L1** (9.6 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), formamide (0.022 mL, 0.6 mmol) were combined with 2.0 mL *tert*-butanol in a 25 mL Schlenk flask. After 4 h the reaction was complete, the reaction cooled to RT, filtered through Celite, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give **32** as 92 mg of a green solid (91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.34 (d, *J* = 4.8 Hz, 1H), 8.01 (s, 1H), 6.93 – 6.77 (m, 5H), 5.44 (s, 2H), 3.74 (s, 3H), 2.43 (s, 3H)

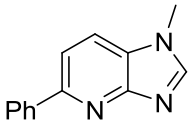
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 159.5, 156.5, 146.2, 145.1, 131.4, 128.3, 127.3, 125.6, 120.8, 114.6, 55.4, 50.3, 17.9

FT-IR (NaCl, thin film) ν = 3053, 2959, 2933, 2837, 1696, 1608, 1586, 1513, 1493, 1357, 1249, 1178, 1031, 821 cm^{-1}.

Anal. Calc $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59; found C, 71.43; H, 5.81; N, 16.61

MP: 105 – 108 °C

R_f (4% MeOH / CH_2Cl_2): 0.20



1-Methyl-5-phenyl-1H-imidazo[4,5-*b*]pyridine (33)

Following the general experimental; 2-chloro-N-methyl-6-phenylpyridin-3-amine (**27**) (87.5 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.14 mg, 0.004 mmol), **L1** (9.6 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), formamide (0.022 mL, 0.6 mmol) were combined with 2.0 mL *tert*-butanol in a 25 mL Schlenk flask. After 3 h the reaction was complete, the reaction cooled to RT, filtered through Celite, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give **33** as 81 mg of a pale brown solid (89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.13 – 8.08 (m, 2H), 7.99 (s, 1H), 7.67 (1/2 AB d, *J* = 8.4 Hz, 1H), 7.64 (1/2 AB d, *J* = 8.4 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.40 – 7.33 (m, 1H), 3.78 (s, 3H)

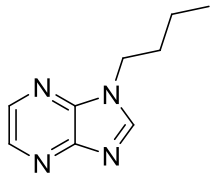
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 156.4, 152.9, 146.1, 139.8, 128.7, 128.5, 127.2, 125.8, 118.2, 115.6, 31.5

FT-IR (NaCl, thin film) ν = 2920, 2852, 1613, 1574, 1495, 1461, 1436, 1407, 1345, 1293, 1199, 1051, 762 cm^{-1}.

Anal. Calc $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08; found C, 74.95; H, 5.49; N, 20.37

MP: 157 – 160 °C

R_f (4% MeOH / CH_2Cl_2): 0.23



1-Butyl-1H-imidazo[4,5-*b*]pyrazine (34)

Following the general experimental; N-butyl-3-chloropyrazin-2-amine (**28**) (74 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.14 mg, 0.004 mmol), *t*-BuBrettphos (9.7 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), formamide (0.022 mL, 0.6 mmol) were combined with 2.0 mL *tert*-butanol in a 25 mL Schlenk flask. After 2 h the reaction was complete, the reaction cooled to RT, filtered through Celite, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give **34** as 70 mg of a yellow solid (99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.50 (d, *J* = 2.7 Hz, 1H), 8.32 – 8.30 (m, 2H), 4.29 (t, *J* = 7.2 Hz, 2H), 1.90 (pent, *J* = 7.5 Hz, 2H), 1.35 (hex, *J* = 7.5 Hz, 2H), 0.93 (t, *J* = 7.5 Hz, 3H)

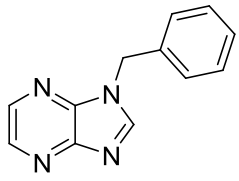
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 146.1, 147.0, 140.1, 140.0, 138.6, 44.2, 31.9, 20.0, 13.6

FT-IR (NaCl, thin film) ν = 3412, 3096, 2057, 2960, 2874, 1655, 1570, 1486, 1464, 1402, 1351, 1196, 850, 757, 638 cm^{-1}.

HRMS (ESI) Calc $(C_9H_{12}N_4)H^+$: 177.1135, Found: 177.1142

MP: 84 - 86°C

R_f (4% MeOH / CH_2Cl_2): 0.23



1-Benzyl-1H-imidazo[4,5-*b*]pyrazine (35)

Following the general experimental; N-benzyl-3-chloropyrazin-2-amine (**29**) (87.9 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.14 mg, 0.004 mmol), *t*-BuBrettPhos (9.7 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), formamide (0.024 mL, 0.6 mmol) were combined with 2 mL *tert*-butanol in a 25 mL Schlenk flask. After 0.5 h the reaction was complete, the reaction cooled to RT, filtered through Celite, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give **35** as 74 mg of a white solid (88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.54 (d, *J* = 2.7 Hz, 1H), 8.35 (d, *J* = 2.4 Hz, 1H), 7.40 – 7.28 (m, 5H), 5.46 (s, 2H)

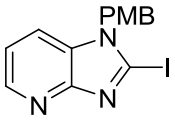
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 149.0, 146.9, 140.3, 139.9, 138.9, 135.0, 129.2, 128.7, 180.0, 47.8

FT-IR (NaCl, thin film) ν = 2020, 2100, 1643, 1483, 1454, 1400, 1353 cm^{-1}.

HRMS (ESI) Calc ($C_{12}H_{10}N_4$): 210.0904, Found: 210.0905

MP: 128-130 °C

R_f (4% MeOH / CH_2Cl_2): 0.27



2-Iodo-1-(4-methoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (36)

To a flame-dried 25 mL RBF equipped with a stirbar was added diisopropylamine (0.60 mL, 4.28 mmol) and THF (6.4 mL). The reaction was cooled to -78 °C (CO_2/acetone) and *n*-BuLi (2.1 mL, 2.0M in hexanes, 4.2 mmol) was added slowly. After 0.5 h 1-(4-methoxybenzyl)-1H-imidazo[4,5-b]pyridine (**25a**) (500 mg, 2.09 mmol) was added as a solution in THF (2.5 mL) and the reaction was stirred for 0.5 h. Next, iodine (1.06 g, 4.2 mmol) was added as a solution in THF (2.1 mL) and the reaction mixture was stirred for 1.5 h. The reaction mixture was removed from the cooling bath and allowed to warm to RT. The reaction was quenched with saturated $Na_2S_2O_{3\,(aq)}$ (5 mL), diluted with EtOAc (10 mL) and stirred for 0.5 h before the layers were separated. The aqueous layer was extracted with EtOAc (3x 20 mL), the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, decanted, and concentrated *in vacuo*. The crude product was purified on a silica gel column (4.5 cm x 12 cm) eluting with 4% MeOH / CH_2Cl_2 to give 640 mg of a brown solid. (84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.48 (dd, *J*= 4.8 Hz, 1.5 Hz, 1H), 7.54 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.12 – 7.05 (m, 3H), 8.85 (dt, *J* = 4.5 Hz, 2.1 Hz, 2H), 5.34 (s, 2H), 3.78 (s, 3H)

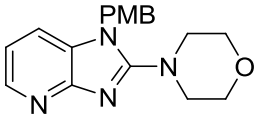
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 159.8, 157.7, 145.3, 128.4, 126.7, 118.4, 118.1, 114.6, 108.3, 55.5, 51.1

FT-IR (NaCl, thin film) ν = 2927, 2835, 1611, 1513, 1404, 1251, 1177, 1030, 764 cm^{-1}.

HRMS (ESI) Calc ($C_{14}H_{12}IN_3O_2$): 365.0022, Found: 365.0025

MP: 125 – 128 °C

R_f (4% MeOH / CH_2Cl_2): 0.27



4-(1-(4-Methoxybenzyl)-1H-imidazo[4,5-*b*]pyridin-2-yl)morpholine (37)

To an oven-dried 25 mL Schlenk tube equipped with a stirbar was added iodide **36** (90 mg, 0.246 mmol) in EtOH (1.3 mL) followed by morpholine(26 μL, 0.296 mmol) and sodium carbonate (39 mg, 0.37 mmol). The reaction was equipped with a cold-finger and heated in a 80°C pre-heated oil-bath for 60 h. The reaction was then cooled to RT, diluted with 3 mL MeOH, filtered through a Celite plug, washing with MeOH (1 mL) and concentrated *in vacuo*. The crude product was purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give 80 mg of a yellow oil (99%).

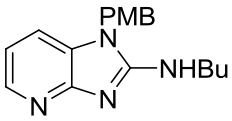
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.32 (dd, *J* = 5.1 Hz, 1.5 Hz, 1H), 7.21 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 2H), 6.95 (dd, *J* = 7.8 Hz, 4.8 Hz, 1H), 6.84 (d, *J* = 6.6 Hz, 2H), 3.81 – 3.75 (m, 4H), 3.37 – 3.32 (m, 4H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 159.6, 159.4, 155.2, 143.7, 128.5, 127.3, 127.2, 116.6 (x2), 114.6, 66.4, 55.4, 50.6, 47.6

FT-IR (NaCl, thin film) ν = 3053, 2962, 2915, 2853, 1612, 1583, 1514, 1411, 1368, 1250, 1177, 1117, 1031, 855, 778 cm^{-1}.

HRMS (ESI) Calc ($C_{18}H_{20}N_4O_2$): 324.1589, Found: 324.1586

R_f (4% MeOH / CH_2Cl_2): 0.24



N-Butyl-1-(4-methoxybenzyl)-1H-imidazo[4,5-*b*]pyridin-2-amine (38)

To an oven-dried 25 mL Schlenk tube equipped with a stirbar was added iodide **36** (35 mg, .096 mmol) in EtOH (0.48 mL) followed by *n*-butyl amine (19 μL, 0.19 mmol) and sodium carbonate (25 mg, 0.24 mmol). The reaction was equipped with a cold-finger and heated in a 80°C pre-heated oil-bath for 72 h. The reaction was then cooled to RT, diluted with H_2O (3 mL) and CH_2Cl_2 (3 mL), the layers separated and the aqueous layer was extracted by CH_2Cl_2 (2 x 3mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give 24.5 mg of a yellow oil (83%).

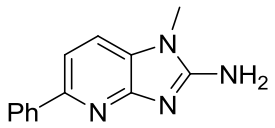
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.20 (br d, *J* = 4.5 Hz, 1H), 7.21 (br d, *J* = 6.9 Hz, 1H), 7.07 (br d, *J* = 8.7 Hz, 2H), 7.00 – 6.80 (m, 3H), 5.02 (s, 2H), 4.43 (br s, 1H), 3.78 (s, 3H), 3.58 – 3.45 (m, 2H), 1.54 (pent, *J* = 7.2 Hz, 2H), 1.25 (sext, *J* = 7.5 Hz), 0.86 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 159.7, 156.4, 142.2, 128.9, 128.0, 127.7, 126.7, 114.8, 114.7, 113.6, 55.5, 45.4, 43.2, 31.8, 20.0, 13.9

FT-IR (NaCl, thin film) ν = 3213, 2957, 2932, 2870, 1611, 1564, 1513, 1oi7ui420, 1247, 1177, 1034, 772 cm^{-1}.

HRMS (ESI) Calc ($C_{18}H_{23}N_4O_1$): 311.1866, Found: 311.1855

R_f (4% MeOH / CH_2Cl_2): 0.24



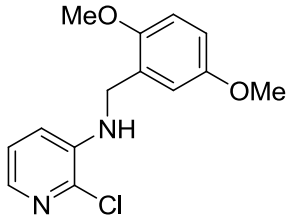
1-Me-5-PhIP (38)[69]

To an oven-dried 25 mL Schlenk tube equipped with a stirbar was added sodamide (213 mg, 5.5 mmol) followed by 1-methyl-5-phenyl-1H-imidazo[4,5-*b*]pyridine **(33)** (52 mg, 0.25 mmol) and of anhydrous *m*-xylene (2.5 mL). The reaction was equipped with a cold-finger, placed in a 130°C pre-heated oil-bath and stirred for 4 h at which time TLC indicated consumption of the azole. The reaction cooled to RT, diluted with CH_2Cl_2 (3 mL) and carefully quenched with water (4 mL). The layers were separated, aqueous layer was extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were dried over MgSO4 and concentrated *in vacuo* to give a red solid. The crude solid was purified on a silica gel column, eluting with 10% MeOH in CH_2Cl_2 to give 53 mg of a yellow solid (95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.05 – 7.99 (m, 2H), 7.53 – 7.38 (m, 4H), 7.34 – 7.28 (m, 1H), 6.97 (br s, 2H), 3.53 (s, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 157.8, 156.5, 148.1, 140.4, 128.4, 127.4, 127.1, 126.1, 114.1, 110.5, 28.9

7.3 2ND GENERATION



2-chloro-N-(2,5-dimethoxybenzyl)pyridin-3-amine (24q)

Following the reductive amination general procedure, 3-amino-2-chloropyridine (2.0 g, 7.78 mmol), 24 mL ethyl acetate, 2,5-dimethoxybenzaldehyde (2.84 g, 17.11 mmol), trifluoroacetic acid (2.31 mL, 31.11 mmol) and sodium triacetoxyborohydride (3.95 g, 18.67 mmol) were combined and stirred for 15 minutes. The reaction was quenched with 20% NaOH and the pH was adjusted with $NaOH_{(s)}$. The layers were separated, the organic layer washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was recrystallized from 40 mL of 5:1 Hexanes:EtOAc to give **24q** as a white crystalline solid (2.8 g, 65%)

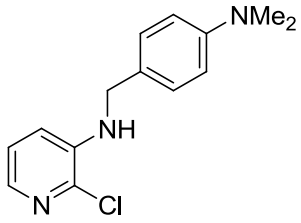
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.69 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 7.03 (dd, *J* = 8.1 Hz, 4.5 Hz, 1H), 6.88 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 6.85-6.74 (m, 3H), 4.92 (br s, 1H), 3.83 (s, 3H), 3.73 (s, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 153.7, 151.6, 140.9, 137.3, 136.6, 127.0, 123.5, 118.1, 115.1, 112.4, 111.4, 55.9, 55.8, 42.8

FT-IR: (NaCl, thin film) ν = 2999, 2943, 2834, 1584, 1495, 1217, 1052, 791 cm^{-1}.

Anal. Calc. $C_{14}H_{15}ClN_2O_2$ C, 60.33; H, 5.42; N, 10.05; found C, 60.14; H, 5.68; N, 9.93

MP: 51-53 °C



2-chloro-N-(4-(dimethylamino)benzylpyridine-3-amine (24r)

Following the reductive amination general procedure, 3-amino-2-chloropyridine (2.0 g, 7.78 mmol), 24 mL ethyl acetate, 4-dimethylaminobenzaldehyde (2.55 g, 17.11 mmol), trifluoroacetic acid (2.31 mL, 31.11 mmol) and sodium triacetoxyborohydride (3.95 g, 18.67 mmol) were combined and stirred for 15 minutes. The reaction was quenched with 20% NaOH and the pH was adjusted with $NaOH_{(s)}$. The layers were separated, the organic layer washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was recrystallized from 30 mL of 2:1 Hexanes:EtOAc to give **24r** as an off-white crystalline solid (2.35 g, 58%)

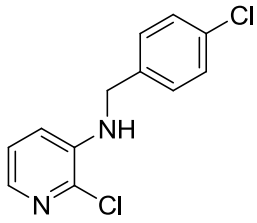
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.69 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.05 (dd, *J* = 7.8 Hz, 4.5 Hz, 1H), 6.89 (dd, *J* = 8.1 Hz, 1.8 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 2H), 4.69 (br s, 1H), 4.26 (d, *J* = 5.4 Hz, 2H), 2.96 (s, 6H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 150.3, 140.9, 137.1, 136.4, 128.5, 125.2, 123.5, 117.8, 112.8, 47.2, 40.7

FT-IR: (NaCl, thin film) ν = 2845, 2798, 1614, 1584, 1524, 1483, 1327, 1205, 1093, 1059, 804 cm^{-1}.

Anal. Calc. $C_{14}H_{16}ClN_3$ C, 64.24; H, 6.16; N, 16.05; found C, 64.58; H, 6.01; N, 15.70

MP: 91-93 °C



2-chloro-N-(4-chlorobenzyl)pyridin-3-amine (24s)

Following the reductive amination general procedure, 3-amino-2-chloropyridine (2.0 g, 7.78 mmol), 24 mL ethyl acetate, p-chlorobenzaldehyde (2.4 g, 17.11 mmol), trifluoroacetic acid (2.31 mL, 31.11 mmol) and sodium triacetoxyborohydride (3.95 g, 18.67 mmol) were combined and stirred for 10 minutes. The reaction was quenched with 20% NaOH and the pH was adjusted with $NaOH_{(s)}$. The layers were separated, the organic layer washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was recrystallized from 80 mL of 15% Hexanes/EtOAc to give **24s** as a white crystalline solid (3.70 g, 99%)

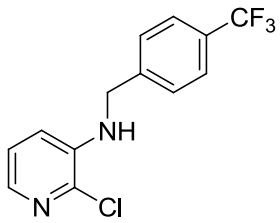
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.73 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.03 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 6.77 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 4.85 (br s, 1H), 4.39 (s, 2H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 140.4, 137.2, 137.0, 136.3, 133.4, 129.1, 128.5, 123.5, 118.0, 46.8

FT-IR: (NaCl, thin film) ν = 3066, 2850, 1584, 1561, 1491, 1381, 1321, 1086, 1054, 796 cm^{-1}.

Anal. Calc. $C_{12}H_{10}Cl_2N_2$ C, 56.94; H, 3.98; N, 11.07; found C,56.72; H, 4.26; N, 11.09

MP: 109-109.5 °C



2-chloro-N-(4-(trifluoromethyl)benzyl)pyridin-3-amine (24t)

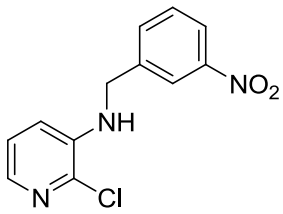
Following the reductive amination general procedure, 3-amino-2-chloropyridine (1.0 g, 7.78 mmol), 24 mL ethyl acetate, *p*-trifluoromethylbenzaldehyde (1.63 g, 9.3 mmol), trifluoroacetic acid (1.16 mL, 15.56 mmol) and sodium triacetoxyborohydride (2.14 g, 10.1 mmol) were combined and stirred for 10 minutes. The reaction was quenched with 20% NaOH and the pH was adjusted with $NaOH_{(s)}$. The layers were separated, the organic layer washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified on a silica gel column eluting with 20% EtOAc / Hexanes to give **2t** as a colorless oil (2.01 g, 90%)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.71 (dd, *J* = 1.8 Hz, 4.8 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 2H), 6.99 (dd, *J* = 4.8 Hz, 8.1 Hz, 1H), 6.73 (dd, *J* = 1.5 Hz, 7.8 Hz, 1H), 4.98 (br s, 1H), 4.47 (d, *J* = 5.7 Hz, 2H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 142.1, 140.3, 137.2, 137.1, 130.0 (q, *J* = 32.2 Hz), 127.2, 125.8 (q, *J* = 4.0 Hz), 124.1 (q, *J* = 270 Hz), 123.5, 118.0, 46.9

FT-IR: (NaCl, thin film) ν = 3065, 2904, 2857, 1919, 1619, 1588, 1503, 1418, 1325, 1097, 1017, 830, 730, 651 cm^{-1}.

Anal. Calc. $C_{13}H_{10}ClF_3N_2$ C, 54.46; H, 3.52; N, 9.49; found C, 54.75; H, 3.36; N, 9.49



2-chloro-N-(3-nitrobenzyl)pyridin-3-amine (24u)

Following the reductive amination general procedure, 3-amino-2-chloropyridine (2.0 g, 15.6 mmol), 24 mL ethyl acetate, 3-nitrobenzaldehyde (2.6 g, 17.1 mmol), trifluoroacetic acid (2.31 mL, 31.11 mmol) and sodium triacetoxyborohydride (3.96 g, 18.67 mmol) were combined and stirred for 3 hours. The reaction was quenched with 20% NaOH and the pH was adjusted with $NaOH_{(s)}$. The layers were separated, the organic layer washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was recrystallized from Hexanes/EtOAc to give **24u** as a yellow crystalline solid (3.9 g, 74%)

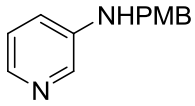
^{1}H NMR (300MHz, $CDCl_3$) δ= 8.22 (d, *J*=1.5 Hz, 1H), 8.12 (dd, *J*=8.1 Hz, 1.2 Hz, 1H), 7.77 (dd, *J*=4.8 Hz, 1.8 Hz, 1H), 7.69 (dd, *J*=7.8 Hz, .6 Hz, 1H), 7.55 (t, *J*=15.9 Hz, 1H) 7.04 (dd, *J*=8.1 Hz, 4.8 Hz, 1H), 6.75 (dd, *J*=8.1 Hz, 1.5 Hz, 1H), 4.54 (s, 2H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 148.8, 140.3, 140.1, 137.6, 137.5, 132.9, 130.1, 123.5, 122.9, 122.0, 118.0, 46.9

FT-IR (NaCl, thin film) ν =3068, 2865, 1585, 1527, 1348, 1056 cm^{-1}

Anal. Calc. $C_{12}H_{10}ClN_3O_2$ C, 54.66; H, 3.82; N, 15.94; found C, 54.77; H, 3.99; N, 15.61

MP: 103-107 °C



N-(4-methoxybenzyl)pyridin-3-amine (39)

To an oven-dried 100 mL round-bottom flask was added 3-aminopyridine (2.5 g, 26.6 mmol) and 41 mL of EtOAc. *p*-Anisaldehyde (3.56 mL, 29.3 mmol) and trifluoroacetic acid (4.07 mL, 53.2 mmol) were added, and the reaction was stirred 10 min. Sodium triacetoxyborohydride (6.8 g, 31.9 mmol) was added portionwise, and the reaction stirred 30 min. Additional sodium triacetoxyborohydride (1g) was added, and the reaction stirred a further 30 min. The reaction was quenched with 1M $NaOH_{(aq)}$ and basified to pH 11 with $NaOH_{(s)}$. The reaction mixture was diluted with EtOAC, and the layers separated. The aqueous layer was extracted with EtOAc (40 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 5.2 g of a yellow solid. The crude solid was recrystallized from EtOAc / Hexanes to give 4.1 g of a white solid. (72%)

^{1}H NMR (300MHz, $CDCl_3$) δ= 8.05 (d, *J* = 2.7 Hz, 1H), 7.95 (dd, *J* = 1.2 Hz, 4.5 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.05 (ddd, *J* = 0.6 Hz, 4.5 Hz, 8.4 Hz, 1H), 6.92 – 6.81 (m, 3H), 4.24 (d, *J* = 5.1 Hz, 2H), 4.14 (br s, 1H), 3.79 (s, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 159.1, 144.2, 139.0, 136.3, 130.6, 128.8, 123.8, 118.6, 114.2, 55.4, 47.4

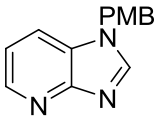
FT-IR (NaCl, thin film) ν = 3229. 1578, 1511, 1414, 1246, 1176, 1031, 796, 707 cm^{-1}

Anal. Calc. $C_{13}H_{14}N_2O$ C, 72.87; H, 6.59; N, 13.07; found C, 72.78; H, 6.36; N, 12.82

MP: 149-151 °C

General Procedure C: Cyclization of 2-Chloro-3-aminopyridines

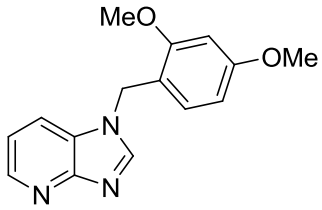
To an oven-dried 25 mL Schlenk tube equipped with a stirbar was added $Pd_2(dba)_3 \cdot CHCl_3$ (1 mol %), XantPhos (5 mol %), K_3PO_4 (1.5 Eq.) and the pyridine (1 Eq.). The reaction vessel was evacuated under vacuum and refilled with $Ar_{(g)}$. 1,4-Dioxane and *t*-AmOH (10:1, 0.2 M) were then added via syringe and the reaction mixture was degassed by three vacuum/$Ar_{(g)}$ purge cycles. The reaction vessel was then equipped with a cold-finger, and placed in a pre-heated 110 °C oil-bath and stirred for the specified time. Upon consumption of the pyridine (as judged by TLC analysis) the reaction was allowed to cool to RT, diluted with methanol, and passed through a Celite plug, washing with additional methanol. The crude product was concentrated *in vacuo*, and applied to a silica gel column, eluting with the specified eluent.



1-(4-methoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (25a)

2-Chloro-N-(4-methoxybenzyl)pyridin-3-amine (100mg, 0.4 mmol) was reacted following general procedure C for 6 h. The crude product was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to yield the product as an off-white solid (89 mg, 93%).

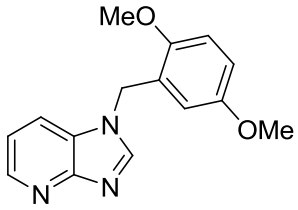
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.50 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 8.11 (s, 1H), 7.54 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.15 – 7.05 (m, 3H), 6.83 (d, 8.7 Hz, 2H), 5.26 (s, 2H), 3.75 (s, 3H)



1-(2,4-Dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (25c)

2-chloro-N-(2,4-dimethoxybenzyl)pyridin-3-amine (279 mg, 1.0 mmol) was reacted following general procedure C for 7 h. The crude product was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to yield the product as a beige solid (217 mg, 81%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.52 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 8.16 (s, 1H), 7.71 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.16 (dd, *J*= 8.1 Hz, 4.8 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 1H), 6.46 – 6.40 (m, 2H), 5.25 (s, 2H), 3.78 (s, 6H)



1-(2,5-Dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (25q)

2-chloro-N-(2,5-dimethoxybenzyl)pyridin-3-amine (112 mg, 0.4 mmol) was reacted following general procedure C for 6.5 h. The crude product was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to yield the product as a beige solid (92 mg, 85%).

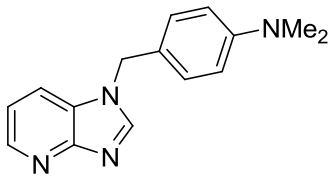
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.48 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 8.15 (s, 1H), 7.68 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.12 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 6.77 (d, *J* = 1.8 Hz, 2H), 6.65 (br s, 1H), 5.25 (s, 2H), 3.74 (s, 3H), 3.66 (s, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 156.3, 153.6, 151.4, 145.8, 144.7, 126.3, 123.9, 118.3, 118.0, 116.0, 113.8, 111.6, 55.8, 55.8, 44.9

FT-IR (NaCl, thin film) ν = 3051, 2951, 2835, 1610, 1504, 1412, 1286, 1227, 1047, 783, 592 cm^{-1}.

EA: Calculated: $C_{15}H_{15}N_3O_2$, C; 66.75; H, 5.61; N, 15.60; found C, 66.75; H, 5.87; N, 15.93

MP: 143 – 144 °C



4-((1H-imidazo[4,5-*b*]pyridin-1-yl)methyl)-N,N-dimethylaniline (25r)

2-Chloro-N-(4-(dimethylamino)benzyl)pyridin-3-amine (105 mg, 0.4 mmol) was reacted following general procedure C for 6.5 h. The crude product was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to yield the product as a beige solid (95 mg, 94%).

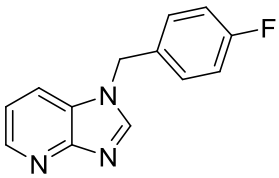
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.48 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 8.08 (s, 1H), 7.57 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.09 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 7.05 (d, *J* = 9 Hz, 2H), 6.62 (d, *J* = 9 Hz, 2H), 5.19 (s, 2H), 2.89 (s, 6H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 156.6, 150.5, 145.2, 144.8, 128.7, 126.2, 121.5, 118.5, 118.0, 112.5, 49.3, 40.4

FT-IR (NaCl, thin film) ν = 3051, 3000, 2951, 2835, 1610, 1503, 1464, 1411, 1286, 1227, 1046, 783 cm^{-1}.

EA: Calculated: $C_{15}H_{16}N_4$, C; 71.40; H, 6.39; N, 22.21; found C, 71.56; H, 6.12; N, 22.35

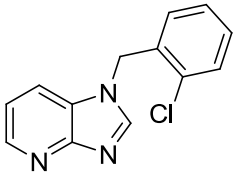
MP: 115 – 119 °C



1-(4-Fluorobenzyl)-1H-imidazo[4,5-*b*]pyridine (25v)

2-chloro-N-(4-fluorobenzyl)pyridin-3-amine (95 mg, 0.4 mmol) was reacted following general procedure C for 6.5 h. The crude product was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to yield the product as a brown solid (87 mg, 96%).

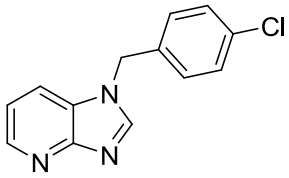
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.48 (dd, *J*=4.8 Hz, 1.8 Hz, 1H) 8.14 (s, 1H), 7.53 (dd, *J*=8.1 Hz, 1.5 Hz, 1H), 7.16-7.10 (m, 3H), 7.01-6.96 (m, 2H), 5.33 (s, 2H)



1-(2-chlorobenzyl)-1H-imidazo[4,5-*b*]pyridine (25e)

2-Chloro-N-(2-chlorobenzyl)pyridin-3-amine (101 mg, 0.4 mmol) was reacted following general procedure C for 6.5 h. The crude product was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to yield the product as a brown solid (77 mg, 79%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.51 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 8.16 (s, 1H), 7.60 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.39 (dd, *J* = 8.1 Hz, 1.2 Hz, 1H), 7.25 (td, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.17 (dd, *J* = XX Hz, 1.2 Hz, 1H), 7.13 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 5.44 (s, 2H)



1-(4-chlorobenzyl)-1H-imidazo[4,5-*b*]pyridine (25s)

2-Chloro-N-(4-chlorobenzyl)pyridin-3-amine (101mg, 0.4 mmol) was reacted following general procedure C for 6.5 h. The crude product was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to yield the product as a white solid (92 mg, 94%).

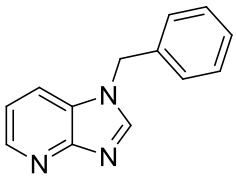
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.50 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 8.14 (s, 1H), 7.50 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.11 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 2H), 5.33 (s, 2H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 156.5, 145.3, 145.2, 134.5, 133.3, 129.4, 128.5, 126.0, 118.4, 118.3, 48.8

FT-IR (NaCl, thin film) ν = 3072, 2973, 1610, 1494, 1409, 1293, 1215, 1176, 1079, 1014, 782 cm^{-1}.

EA: Calculated: $C_{13}H_{10}ClN_3$, C; 64.07; H, 4.14; N, 17.24; found C, 64.20; H, 3.99; N, 17.05

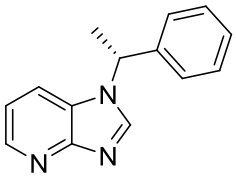
MP: 134 – 136 °C



1-benzyl-1H-imidazo[4,5-*b*]pyridine (25b)

N-benzyl-2-chloropyridin-3-amine (85 mg, 0.4 mmol) was reacted following general procedure C for 6.5 h. The crude product was purified by flash column chromatography (4% MeOH in CH_2Cl_2) to yield the product as a brown solid (71 mg, 85%).

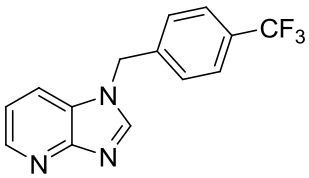
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.50 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 8.14 (s, 1H), 7.53 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.34 – 7.24 (m, 3H), 7.18 – 7.08 (m, 3H), 5.34 (s, 2H)



***(R)*-1-(1-Phenylethyl)-1H-imidazo[4,5-*b*]pyridine (25m)**

(R)-2-chloro-N-(1-phenylethyl)pyridin-3-amine (93 mg, 0.4 mmol) was reacted following general procedure C for 6.5 h. The crude product was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to yield the product as a brown solid (85 mg, 96%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.52 (dd, *J* = 4.5 Hz, 1.5 Hz, 1H), 8.30 (s, 1H), 7.43 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.37 – 7.28 (m, 3H), 7.19 – 7.14 (m, 2H), 7.08 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 5.61 (q, *J* = 7.2 Hz, 1H), 2.00 (d, *J* = 6.9 Hz, 3H)



1-(4-(trifluoromethyl)benzyl)-1H-imidazo[4,5-*b*]pyridine (25t)

2-chloro-N-(4-(trifluoromethyl)benzyl)pyridin-3-amine (115 mg, 0.4 mmol) was reacted following general procedure C for 7 h. The crude product was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to yield the product as a beige solid (105 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.54 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 8.19 (s, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.51 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.15 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 5.46 (s, 2H)

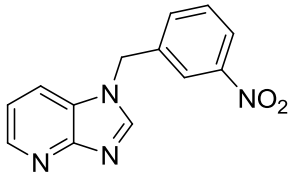
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 156.6, 145.4, 138.9, 131.0 (q, J_{C-F} = 32.5 Hz), 127.4, 126.3 (q, J_{C-F} = 3.8 Hz), 126.1, 123.8(q, J_{C-F} = 270.8 Hz), 118.5, 118.3, 48.9

^{19}F NMR (282.4 MHz, $CDCl_3$) δ= - 63.2

FT-IR (NaCl, thin film) ν = 3083, 2053, 3023, 2978, 1612, 1495, 1329, 1290, 1159, 1065, 1017, 782 cm^{-1}.

EA: Calculated: $C_{14}H_{19}N_3F_3$, C; 60.65; H, 3.64; N, 15.16; found C, 60.20; H, 3.61; N, 15.20

MP: 159 – 160 °C



1-(3-nitrobenzyl)-1H-imidazo[4,5-*b*]pyridine (25u)

2-chloro-N-(3-nitrobenzyl)pyridin-3-amine (105 mg, 0.4 mmol) was reacted following general procedure C for 6.5 h. The crude product was purified by flash column chromatography (4 % MeOH in CH_2Cl_2) to yield the product as a brown solid (58 mg, 57%).

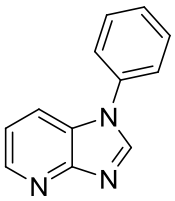
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.57 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 8.25 (s, 1H), 8.21 – 8.15 (m, 1H), 8.12 (app t, *J* = 1.8 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.46 – 7.41 (m, 1H), 7.18 (dd, *J* = 8.1 Hz, 4.5 Hz, 1H), 5.53 (s, 2H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 156.6, 148.8, 145.6, 145.3, 137.1, 132.9, 130.6, 125.9, 123.8, 122.2, 118.7, 118.2, 48.7

FT-IR (NaCl, thin film) ν = 3051, 2927, 2852, 1610, 1529, 1493, 1413, 1349, 1291, 1212, 728 cm^{-1}.

EA: Calculated: $C_{13}H_{10}N_4O_2$, C; 61.41; H, 3.96; N, 22.04; found C, 61.13; H, 3.86; N, 22.41

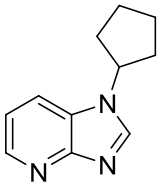
MP: 115 – 118 °C



1-Phenyl-1H-imidazo[4,5-*b*]pyridine (25o)

2-Chloro-N-phenylpyridin-3-amine (82 mg, 0.4 mmol) was reacted following general procedure C for 6 h. The crude product was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to yield the product as a white solid (73 mg, 94%).

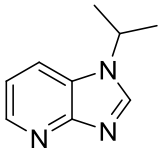
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.57 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 8.30 (s, 1H), 7.81 (dd, *J* = 8.4 Hz, 1.8 Hz, 1H), 7.60 – 7.51 (m, 2H), 7.49 – 7.41 (m, 3H), 7.21 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H)



1-cyclopentyl-1H-imidazo[4,5-*b*]pyridine (25j)

2-chloro-N-cyclopentylpyridin-3-amine (80 mg, 0.4 mmol) was reacted following general procedure C for 6.5 h. The crude product was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to yield the product as an off-white solid (64 mg, 85%).

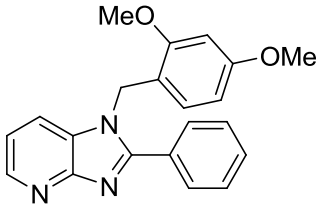
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.51 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 8.14 (s, 1H), 7.74 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.18 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 4.71 (pent, *J* = 6.9 Hz, 1H), 2.35 – 2.15 (m, 2H), 2.05 – 1.70 (m, 6H)



1-isopropyl-1H-imidazo[4,5-*b*]pyridine (25h)

2-chloro-N-isopropylpyridin-3-amine (68 mg, 0.4 mmol) was reacted following general procedure C for 6.5 h. The crude product was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to yield the product as an off-white solid (59 mg, 91%).

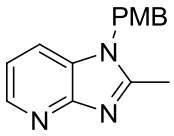
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.53 (dd, *J* = 4.5 Hz, 1.2 Hz, 1H), 8.19 (s, 1H), 7.75 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.20 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 4.63 (sept, *J* = 6.6 Hz, 1H), 1.61 (d, *J* = 6.6 Hz, 6H)



1-(2,4-dimethoxybenzyl)-2-phenyl-1H-imidazo[4,5-*b*]pyridine (30)

To an oven-dried 25 mL Schlenk tube equipped with a stirbar was added $Pd_2(dba)_3 \cdot CHCl_3$ (4.1 mg, 0.004 mmol), XantPhos (12 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol) and the 2-chloro-N-(2,4-dimethoxybenzyl)pyridin-3-amine (112 mg, 1.0 mmol). The reaction vessel was evacuated under vacuum and refilled with $Ar_{(g)}$. Benzamide (73 mg, 0.6 mmol) was added followed by 1,4-Dioxane and *t*-AmOH (10:1, 0.2 M) and the reaction mixture was degassed by three vacuum/$Ar_{(g)}$ purge cycles. The reaction vessel was then equipped with a cold-finger, and placed in a pre-heated 110 °C oil-bath and stirred for 18h. The reaction was then allowed to cool to RT, diluted with methanol, and passed through a Celite plug, washing with additional methanol. The crude product was concentrated *in vacuo*, and purified on a silica gel column, eluting with 3.5 % MeOH / CH_2Cl_2 to give the product as a pale yellow solid (108 mg, 78%).

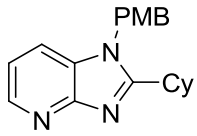
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.54 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 7.86-7.74 (m, 2H), 7.53-7.36 (m, 4H), 7.11 (dd, *J* = 7.8 Hz, 4.8 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.32 (dd, *J* = 8.4 Hz, 2.4 Hz), 5.39 (s, 2H), 3.77 (s, 6H)



1-(4-methoxybenzyl)-2-methyl-1H-imidazo[4,5-*b*]pyridine (31)

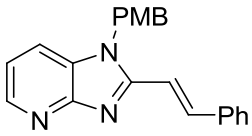
To an oven-dried 25 mL Schlenk tube equipped with a stirbar was added $Pd_2(dba)_3 \cdot CHCl_3$ (4.1 mg, 0.004 mmol), XantPhos (12 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol) and the 2-chloro-N-(4-methoxybenzyl)pyridin-3-amine (100 mg, 1.0 mmol). The reaction vessel was evacuated under vacuum and refilled with $Ar_{(g)}$. Acetamide (35 mg, 0.6 mmol) was added followed by 1,4-Dioxane and *t*-AmOH (10:1, 0.2 M) and the reaction mixture was degassed by three vacuum/$Ar_{(g)}$ purge cycles. The reaction vessel was then equipped with a cold-finger, and placed in a pre-heated 110 °C oil-bath and stirred for 18h. The reaction was then allowed to cool to RT, diluted with methanol, and passed through a Celite plug, washing with additional methanol. The crude product was concentrated *in vacuo*, and applied to a silica gel column, eluting with 3.5 % MeOH / CH_2Cl_2 to give the product as a off-white solid (84 mg, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.47 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 7.48 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.08 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 6.97 (d, *J* = 9 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.25 (s, 2H), 3.76 (s, 3H), 2.62 (s, 3H)



2-Cyclohexyl-1-(4-methoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (47)

To an oven-dried 25 mL Schlenk tube equipped with a stirbar was added $Pd_2(dba)_3 \cdot CHCl_3$ (4.1 mg, 0.004 mmol), XantPhos (12 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol) and the 2-chloro-N-(4-methoxybenzyl)pyridin-3-amine (100 mg, 1.0 mmol). The reaction vessel was evacuated under vacuum and refilled with $Ar_{(g)}$. Cyclohexanecarboxamide (76 mg, 0.6 mmol) was then added followed by 1,4-Dioxane and *t*-AmOH (10:1, 0.2 M) and the reaction mixture was degassed by three vacuum/$Ar_{(g)}$ purge cycles. The reaction vessel was then equipped with a cold-finger, and placed in a pre-heated 110 °C oil-bath and stirred for 24h. The reaction mixture was then allowed to cool to RT, diluted with methanol, and passed through a Celite plug washing with additional methanol. The crude product was concentrated *in vacuo*, and purified on a silica gel column, eluting with 3.5 % MeOH / CH_2Cl_2 to give the product as an off-white solid (57 mg, 44%). Which was a 3:1 mixure of the desired product and cyclohexanecarboxamide; all attempts at further purification were unsuccessful.



(E)-1-(4-methoxybenzyl)-2-styryl-1H-imidazo[4,5-*b*]pyridine (48)

To an oven-dried 25 mL Schlenk tube equipped with a stirbar was added $Pd_2(dba)_3 \cdot CHCl_3$ (4.1 mg, 0.004 mmol), XantPhos (12 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol) and the 2-chloro-N-(4-methoxybenzyl)pyridin-3-amine (100 mg, 1.0 mmol). The reaction vessel was evacuated under vacuum and refilled with $Ar_{(g)}$. *Trans*-Cinnamamide (88 mg, 0.6 mmol) was then added followed by 1,4-Dioxane and *t*-AmOH (10:1, 0.2 M) and the reaction mixture was degassed by three vacuum/$Ar_{(g)}$ purge cycles. The reaction vessel was then equipped with a cold-finger, and placed in a pre-heated 110 °C oil-bath and stirred for 24h. The reaction mixture was then allowed to cool to RT, diluted with methanol, and passed through a Celite plug, washing with additional methanol. The crude product was concentrated *in vacuo*, and purified on a silica gel column, eluting with 3.5 % MeOH / CH_2Cl_2 to give the product as a fluffy pale-yellow solid (130 mg, 96%).

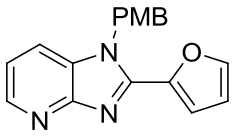
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.48 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 8.11 (d, *J* = 15.9 Hz, 1H), 7.53 – 7.42 (m, 3H), 7.47 – 7.28 (m, 3H), 7.05 – 6.95 (m, 4H), 6.69 (d, *J* = 6.6 Hz, 2H), 5.34 (s, 2H), 3.71 (s, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 159.4, 155.9, 153.2, 145.4, 139.2, 135.6, 129.5, 128.9, 128.0, 127.7, 127.5, 127.5, 117.6, 117.4, 114.5, 112.3, 55.3, 46.5

FT-IR (NaCl, thin film) ν = 2957, 2934, 2836, 1634, 1611, 1513, 1409, 1251, 1177, 1032m 909 cm^{-1}.

EA: Calculated: $C_{22}H_{19}N_3O$, C; 77.40; H, 5.61; N, 12.31; found C, 77.62; H, 5.89; N, 12.49

MP: 123 – 124 °C



2-(furan-2-yl)-1-(4-methoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (46)

To an oven-dried 25 mL Schlenk tube equipped with a stirbar was added $Pd_2(dba)_3{\cdot}CHCl_3$ (4.1 mg, 0.004 mmol), XantPhos (12 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol) and the 2-chloro-N-(4-methoxybenzyl)pyridin-3-amine (100 mg, 1.0 mmol). The reaction vessel was evacuated under vacuum and refilled with $Ar_{(g)}$. 2-Furanamide (67 mg, 0.6 mmol) was then added followed by 1,4-Dioxane and *t*-AmOH (10:1, 0.2 M) and the reaction mixture was degassed by three vacuum/$Ar_{(g)}$ purge cycles. The reaction vessel was then equipped with a cold-finger, and placed in a pre-heated 110 °C oil-bath and stirred for 24h. The reaction was then allowed to cool to RT, diluted with methanol, and passed through a Celite plug, washing with additional methanol. The crude product was concentrated *in vacuo*, and purified on a silica gel column, eluting with 3.5 % MeOH / CH_2Cl_2 to give the product as a white solid (118 mg, 97%).

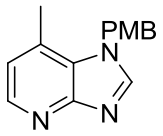
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.50 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 7.57 (dd, *J* = 1.8 Hz, 0.6 Hz, 1H), 7.52 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.29 (dd, *J* = 3.6 Hz, 0.9 Hz, 1H), 7.08 (dd, *J* = 8.1 Hz, 4.8 Hz, 7.03 (d, *J* = 6.6 Hz, 2H), 6.78 (d, *J* = 6.6 Hz, 2H), 6.56 (dd, *J* = 3.3 Hz, 1.8 Hz, 1H), 5.64 (s, 2H), 3.72 (s, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 159.2, 155.5, 146.0, 145.4, 144.9, 144.6, 144.3, 128.0, 127.8, 118.1, 118.0, 114.9, 114.3, 112.3, 55.2, 48.2

FT-IR (NaCl, thin film) ν = 3124, 2933, 2836, 1676, 1610, 1512, 1410, 1382, 1251, 1029, 912 cm^{-1}.

EA: Calculated: $C_{18}H_{15}N_3O_2$, C; 70.81; H, 4.95; N, 13.76; found C, 70.88; H, 5.08; N, 14.01

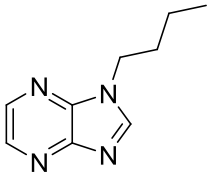
MP: 121 – 124 °C



1-(4-methoxybenzyl)-7-methyl-1H-imidazo[4,5-*b*]pyridine (32)

To an oven-dried 25 mL Schlenk tube equipped with a stirbar was added $Pd_2(dba)_3 \cdot CHCl_3$ (4.1 mg, 0.004 mmol), XantPhos (12 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol) and the 2-chloro-N-(4-methoxybenzyl)-4-methylpyridin-3-amine (112 mg, 1.0 mmol). The reaction vessel was evacuated under vacuum and refilled with $Ar_{(g)}$. Formamide (27 mg, 0.6 mmol) was then added followed by 1,4-Dioxane and *t*-AmOH (10:1, 0.2 M) and the reaction mixture was degassed by three vacuum/$Ar_{(g)}$ purge cycles. The reaction vessel was then equipped with a cold-finger, and placed in a pre-heated 110 °C oil-bath and stirred for 24h. The reaction mixture was then allowed to cool to RT, diluted with methanol, and passed through a Celite plug, washing with additional methanol. The crude product was concentrated *in vacuo*, and purified on a silica gel column, eluting with 3 % MeOH in CH_2Cl_2 to give the product as a yellow solid (71 mg, 70%).

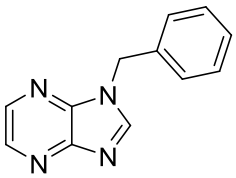
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.39 (d, *J* = 4.8 Hz, 1H), 8.07 (s, 1H), 6.95 – 6.89 (m, 3H), 6.83 (d, *J* = 6.3 Hz, 2H), 5.48 (s, 2H), 3.76 (s, 3H), 2.46 (s, 3H)



1-butyl-1H-imidazo[4,5-*b*]pyrazine (34)

To an oven-dried 25 mL Schlenk tube equipped with a stirbar was added $Pd_2(dba)_3 \cdot CHCl_3$ (4.1 mg, 0.004 mmol), XantPhos (12 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol) and the N-butyl-3-chloropyrazin-2-amine (74 mg, 1.0 mmol). The reaction vessel was evacuated under vacuum and refilled with $Ar_{(g)}$. Formamide (27 mg, 0.6 mmol) was then added followed by 1,4-Dioxane and *t*-AmOH (10:1, 0.2 M) and the reaction mixture was degassed by three vacuum/$Ar_{(g)}$ purge cycles. The reaction vessel was then equipped with a cold-finger, and placed in a pre-heated 110 °C oil-bath and stirred for 2h. The reaction was then allowed to cool to RT, diluted with methanol, and passed through a Celite plug, washing with additional methanol. The crude product was concentrated *in vacuo*, and applied to a silica gel column, eluting with 4 % MeOH in CH_2Cl_2 to give the product as a yellow solid (58 mg, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.51 (d, *J* = 2.7 Hz, 1H), 8.32 – 8.30 (m, 2H), 4.29 (t, *J* = 7.2 Hz, 2H), 1.91 (pent, *J* = 7.5 Hz, 2H), 1.35 (hex, *J* = 7.5 Hz, 2H), 0.94 (t, *J* = 7.5 Hz, 3H)

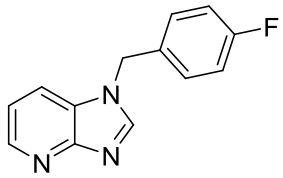


1-benzyl-1H-imidazo[4,5-*b*]pyrazine (35)

To an oven-dried 25 mL Schlenk tube equipped with a stirbar was added $Pd_2(dba)_3 \cdot CHCl_3$ (4.1 mg, 0.004 mmol), XantPhos (12 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol) and the N-benzyl-3-chloropyrazin-2-amine (88 mg, 1.0 mmol). The reaction vessel was evacuated under vacuum and refilled with $Ar_{(g)}$. Formamide (27 mg, 0.6 mmol) was then added followed by 1,4-Dioxane & *t*-AmOH (10:1, 0.2 M) and the reaction mixture was degassed by three vacuum/$Ar_{(g)}$ purge cycles. The reaction vessel was then equipped with a cold-finger, and placed in a pre-heated 110 °C oil-bath and stirred for 1h. The reaction mixture was then allowed to cool to RT, diluted with methanol, and passed through a Celite plug, washing with additional methanol. The crude product was concentrated *in vacuo*, and purified on a silica gel column, eluting with 3 % MeOH in CH_2Cl_2 to give the product as a yellow solid (80 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.52 (d, *J* = 2.7 Hz, 1H), 8.34 (d, *J* = 2.7 Hz, 1H), 8.31 (s, 1H), 7.35 – 7.26 (m, 5H), 5.45 (s, 2H)

7.4 SNAR



1-(4-Fluorobenzyl)-1H-imidazo[4,5-*b*]pyridine (SI3)

To an oven-dried 25 mL Schlenk tube equipped with a magnetic stirbar was added 2-chloro-N-(4-fluorobenzyl)pyridin-3-amine[50] (95 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4.2 mg, 0.004 mmol), $Me_3(OMe)$*t*-BuXPhos (9.9 mg, 0.02 mmol), and K_3PO_4 (128 mg, 0.6 mmol). The tube was evacuated and refilled with $Ar_{(g)}$ at which time formamide (24 μL, 6.3 mmol) and 2 mL *tert*-butanol were added. The reaction vessel was then subjected to three vacuum / $Ar_{(g)}$ purge cycles and placed into a preheated 120 °C oil-bath. The reaction mixture was stirred for 3.5 h at which time TLC analysis indicated the chloropyridine was consumed. The reaction mixture was cooled to RT, filtered through a Celite plug, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm), eluting with 4% MeOH / CH_2Cl_2 to give 87 mg (96%) as a brown solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.57 (dd, *J*=4.8 Hz, 1.8 Hz, 1H) 8.17 (s, 1H), 7.55 (dd, *J*=8.1 Hz, 1.5 Hz, 1H), 7.19-7.14 (m, 3H), 7.08-7.01 (m, 2H), 5.35 (s, 2H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 162.8 (d, *J*=247.7 Hz), 156.6, 145.3, 145.2, 130.6 (d, *J*=3.3 Hz), 129.1 (d, *J*= 8.4 Hz), 126.1, 118.4, 118.3, 116.3 (d, *J* = 21.8 Hz), 48.9

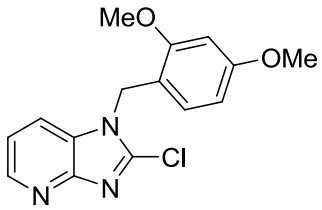
^{19}F NMR (282.4 MHz, $CDCl_3$) δ= -113.3 —-113.4 (m)

FT-IR: (NaCl, thin film) ν = 3054, 1609, 1510, 1492, 1414, 1361, 1292, 1223, 1158, 780 cm^{-1}.

EA: Calculated: C 68.71, H 4.44, N 18.49; Found: C 68.50, H 4.78, N 18.20

MP: 86-89°C

General Procedure D: Chlorination



2-chloro-1-(2,4-dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (49a)[77]

To a flame-dried 50 mL RBF equipped with a magnetic stirbar was added 14.9 mL of THF and diisopropylamine (1.07 mL, 7.64 mmol). The reaction mixture was cooled to -78 °C (CO_2/acetone), *n*-BuLi (3.82 mL, 1.95M in hexanes, 7.46 mmol) was added slowly, and the reaction mixutre stirred for 1h at which time 1-(4-methoxybenzyl)-1H-imidazo[4,5-*b*]pyridine[74] (1.0 g, 3.73 mmol) was added as a solution in 7.5 mL of THF. The reaction mixutre was stirred for 1 h at which time hexachloroethane (1.77 g, 7.46 mmol) was added at -78°C as a solution in 4 mL of THF. The reaction mixutre was stirred for 2 h at -78 °C, warmed to RT and stirred for an additional 0.5 h. At this time the reaction was quenched with 2 mL of $NH_4Cl_{(aq)}$, diluted with 10 mL of H_2O and poured into 20 mL of EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified on a silica gel column (4.5 cm x 12 cm) eluting with 3% MeOH / CH_2Cl_2 to give 920 mg of an oil that solidified to a brown solid when triturated with 5 mL of MeCN. (81%)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.50 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 7.59 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.14 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.45 – 6.39 (m, 2H), 5.33 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H)

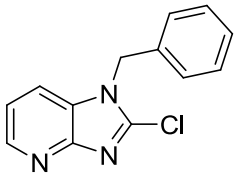
^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 161.2, 158.1, 153.9, 144.9, 144.3, 129.9, 128.0, 118.5, 118.2, 114.8, 104.2, 98.5, 55.4, 55.3, 43.8

FT-IR: (NaCl, thin film) ν = 2939, 2837, 1612, 1589, 1509, 1463, 1410, 1371, 1278, 1210, 1033, 834, 781 cm^{-1}.

HRMS (ESI) Calc ($C_{15}H_{14}ClN_3O_2$)Na+:, 326.0667 Found: 326.0671

MP: 92 – 93 °C

R_f (4% MeOH / CH_2Cl_2): 0.24



1-Benzyl-2-chloro-1H-imidazo[4,5-*b*]pyridine (49b)

Following general procedure D 6.64 mL of THF and diisopropylamine (0.47 mL, 3.32 mmol) were combined and the reaction mixture was cooled to -78°C. *n*-BuLi (1.3 mL, 2.5M, 3.24 mmol) was added, the reaction mixture was stirred for 1 h at which time 1-benzyl-1H-imidazo[4,5-*b*]pyridine[74] (340 mg, 1.62 mmol) was added as a solution in 3.2 mL of THF. The reaction mixture was stirred for 1 h at which time hexachloroethane (767 mg, 3.24 mmol) was added as a solution in 1.7 mL of THF. the reaction mixture stirred for 2 h at -78°C and then allowed to warm to rt over 0.5 h. At this time the reaction was quenched with 2 mL of $NH_4Cl_{(aq)}$, diluted with 9 mL of H_2O and poured into 20 mL of EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified on a silica gel column (4.5 cm x 12 cm) eluting with 4% MeOH / CH_2Cl_2 to give 244 mg of a red-brown solid. (62 %)

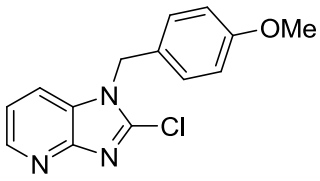
^{1}H NMR: (300 MHz, $CDCl_3$) δ= 8.46 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 7.49 (dd, *J* = 8.1 Hz, 1.2 Hz, 1H), 7.30-7.27 (m, 3H) 7.14-7.09 (m, 3H), 5.37 (s, 2H)

^{13}C NMR: (75.4 MHz, $CDCl_3$) δ= 154.1, 145.3, 144.0, 134.3, 129.2, 128.5, 127.8, 126.9, 118.6, 118.0, 48.3

FT-IR: (NaCl, thin film) ν = 2964, 1608, 1460, 1415, 1361, 1313, 1276, 1187, 781, 726, 696 cm^{-1}.

HRMS Calc $(C_{13}H_{10}ClN_3)H^+$: 244.0636, Found: 244.0635

MP: 164-167° C



2-chloro-1-(4-Methoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (49c)

Following general procedure D, 5.14 mL of THF, diisopropylamine (0.36 mL, 2.57 mmol), *n*-BuLi (1.0 mL, 2.4M, 2.5 mmol), 1-(4-Methoxybenzyl)-1H-imidazo[4,5-*b*]pyridine[74] (300 mg, 1.25 mmol) as a solution in 2.5 mL of THF, and hexachloroethane (0.59 g, 2.5 mmol) as a solution in 1.3 mL of THF was added to a flame dried 50 mL RBF. The reaction mixture stirred for 1.5 h at -78 °C and warmed to RT. The reaction mixture was quenched with 2 mL of sat. $NH_4Cl_{(aq)}$, diluted with 10 mL of H_2O, and poured into 20 mL of EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified on a silica column (2.5 cm x 12 cm) eluting with 3% MeOH / CH_2Cl_2 to give 0.168 g (49%) as a gold crystalline solid.

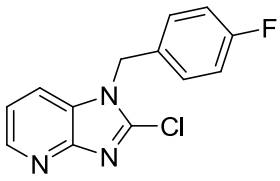
^{1}H NMR (300 MHz, $CDCl_3$) δ=8.53 (dd, *J*=4.8 Hz, 1.5 Hz, 1H), 7.54 (dd, *J*=8.1 Hz, 1.5 Hz, 1H), 7.20-7.12 (m, 3H), 6.86 (d, *J*=9 Hz, 2H), 5.35 (s, 2H), 3.78 (s, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 159.7, 154.1, 145.3, 144.0, 128.5, 127.7, 126.3, 118.6, 118.1, 114.5, 55.3, 47.9

FT-IR (NaCl, thin film) ν = 2355, 1611, 1513, 1463, 1370, 1250 cm^{-1}.

Anal: Calculated: C 61.43, H 4.42, N 15.35; Found: C 61.63, H 4.67, N, 15.26

MP: 138-141 °C



2-Chloro-1-(4-fluorobenzyl)-1H-imidazo[4,5-*b*]pyridine (49d)

Following general procedure D, 35.3 mL of THF, diisopropylamine (0.37 mL, 2.67 mmol), *n*-BuLi (1.5 mL, 1.75M, 2.6 mmol), 1-(4-Fluorobenzyl)-1H-imidazo[4,5-*b*]pyridine (**SI3**) (300 mg, 1.3 mmol) as a solution in 1.75 mL of THF, hexachloroethane (0.61 g, 2.6 mmol) as a solution in 1.4 mL of THF was added to an oven dried 50 mL RBF. The reaction mixture stirred for 1 h at -78 °C, warmed to RT and stirred for 0.5 h. The reaction mixture was quenched with 2 mL of sat. $NH_4Cl_{(aq)}$, diluted with 8 mL of H_2O, and poured into 20 mL of EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified on a silica column (2.5 cm x 12 cm) eluting with 3% MeOH / CH_2Cl_2 to give 0.211 g (61%) as a light brown solid.

^{1}H NMR (300MHz, $CDCl_3$) δ= 8.46 (dd, *J* =4.8 Hz, 0.9 Hz, 1H), 7.51, (dd, *J* =8.1 Hz, 0.9 Hz, 1H), 7.15-7.11 (m, 3H), 6.97 (t, *J*=15.3, 2H), 5.35 (s, 2H)

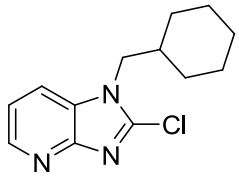
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 162.7 (d, *J* = 247.6 Hz), 154.2, 145.5, 143.9, 130.2 (d, *J*= 3.2 Hz), 128.9 (d, *J* = 8.3 Hz), 127.7, 118.8, 117.9, 116.3 (d, *J* = 21.8 Hz), 47.7

^{19}F NMR (282.4 MHz, $CDCl_3$) δ= -113.27 — -113.37 (m)

FT-IR (NaCl, thin film) ν = 1643, 1511, 1464, 1371, 1277, 1224 cm^{-1}.

Anal: Calculated: C 59.67, H 3.47, N 16.06; Found: C 59.43, H 3.57, N 16.04

MP: 130-132°C



2-Chloro-1-(cyclohexylmethyl)-1H-imidazo[4,5-*b*]pyridine (49c)

Following general procedure D, 1.88 mL of THF, diisopropylamine (0.13 mL, 0.94 mmol), *n*-BuLi (0.43 mL, 2.15M, 0.92 mmol), 1-(cyclohexylmethyl)-1H-imidazo[4,5-*b*]pyridine[74] (100 mg, 0.46 mmol) as a solution in 0.92 mL of THF, hexachloroethane (0.23 g, 0.92 mmol) as a solution in 0.49 mL of THF was added to an flame dried 25 mL RBF. The reaction mixture stirred for 2 h at -78 °C, warmed to RT and stirred for 15 min. The reaction mixture was quenched with 2 mL of sat. $NH_4Cl_{(aq)}$, diluted with 7 mL of H_2O, and poured into 15 mL of EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified on a silica column (2.5 cm x 12 cm) eluting with 3% MeOH / CH_2Cl_2 to give 78.2 mg (69%) as a green solid.

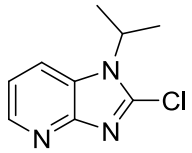
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.48 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 7.60 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.18 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 3.99 (d, *J* = 7.2 Hz, 2H), 1.88-1.57 (m, 6H), 1.18-1.00 (m, 5H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 153.9, 145.1, 144.2, 128.3, 118.4, 117.9, 50.9, 38.3, 30.8, 26.0, 25.6

FT-IR (NaCl, thin film) ν = 2926, 2852, 1466, 1414, 1378 cm^{-1}.

EA: Calculated: C 62.52, H 6.46, N 16.83; Found: C 62.72, H 6.41, N 16.66

MP: 130-133°C



2-chloro-1-isopropyl-1*H*-imidazo[4,5-*b*]pyridine (49f)

Following general procedure D, 2.5 mL of THF, diisopropylamine (0.179 mL, 1.27 mmol) were added, then cooled to -78 °C (CO_2/acetone), *n*-BuLi (0.58 mL, 2.15M, 1.24 mmol) was added slowly, the reaction mixture stirred for 1 h and 1-isopropyl-1*H*-imidazo[4,5-*b*]pyridine[74] (100 mg, 0.62 mmol) was added as a solution in 2.4 mL of THF. The reaction mixture was stirred for 50 min at which time hexachloroethane (294 mg, 1.24 mmol) was added at -78°C as a solution in 0.65 mL of THF. The reaction mixture was stirred 1.5 h at -78 °C, warmed to RT over 0.5 h. At this time the reaction was quenched with 2 mL of $NH_4Cl_{(aq)}$, diluted with 5 mL of H_2O and poured into 15 mL of EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with H_2O, brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified on a silica gel column (2.5 cm x 12 cm) eluting with 4% MeOH / CH_2Cl to give 83 mg of a red/brown solid. (69%)

^{1}H NMR: (300 MHz, $CDCl_3$) δ= 8.46 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 7.79 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.15 (dd, *J* = 8.4 Hz, 4.8 Hz, 1H), 4.96-4.86 (m, 1H), 1.61, (d, *J* = 4.5 Hz, 6H)

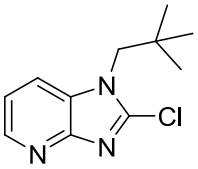
^{13}C NMR: (75.4 MHz, $CDCl_3$) δ= 154.3, 144.9, 143.2, 126.2, 119.0, 118.0, 49.7, 21.3

FT-IR: (NaCl, thin film) ν = 2984, 1647, 1454, 1409, 1354, 1298, 783 cm^{-1}.

HRMS Calc $(C_9H_{10}ClN_3)H^+$: 196.0636, Found: 196.0636

MP: 67-70 °C

2-Chloro-1-neopentyl-1*H*-imidazo[4,5-*b*]pyridine (49g)



Following general procedure D, 4.76 mL of THF, diisopropylamine (0.335 mL, 2.38 mmol) were added then cooled to -78 °C (CO_2/acetone) and, *n*-BuLi (1.19 mL, 2.15M, 2.32 mmol) was added slowly, the reaction mixture stirred for 1 h and 1-neopentyl-1H-imidazo[4,5-*b*]pyridine[74] (220 mg, 1.16 mmol) was added as a solution in 2.4 mL of THF. The reaction mixture was stirred for 50 min at which time hexachloroethane (550 mg, 2.32 mmol) was added at -78°C as a solution in 1.3 mL of THF. The reaction mixture was stirred 1 h at -78 °C, warmed to RT over 0.5 h. At this time the reaction was quenched with 2 mL of sat. $NH_4Cl_{(aq)}$, diluted with 15 mL of H_2O and poured into 20 mL of EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with H_2O, brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified on a silica gel column (4.5 cm x 12 cm) eluting with 4% MeOH / CH_2Cl_2 to give 136 mg of a brown solid. (52%)

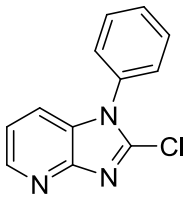
^{1}H NMR: (300 MHz, $CDCl_3$) δ= 8.49 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 7.64 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.18 (dd, *J* = 8.1 Hz, 4.5 Hz, 1H), 4.00 (s, 2H), 1.03 (s, 9H)

^{13}C NMR: (75.4 MHz, $CDCl_3$) δ= 154.0, 145.2, 145.1, 129.0, 118.9, 118.4, 56.0, 35.1, 28.5

FT-IR: (NaCl, thin film) ν = 3053, 2966, 2874, 1605, 1463, 1412, 1400, 1374, 1285, 1175, 797, 784 cm^{-1}.

Anal. Calc. $C_{11}H_{14}ClN_3$ C, 59.06; H, 6.31; N, 18.78; found C, 58.88; H, 6.11; N, 18.70

MP: 121-125 °C



2-Chloro-1-phenyl-1*H*-imidazo[4,5-*b*]pyridine (49h)

Following general procedure D, 6.3 mL of THF, diisopropylamine (0.44 mL, 3.16 mmol) were added, then cooled to -78 °C (CO_2/acetone) and, *n*-BuLi (1.43 mL, 2.15M, 3.08 mmol) was added slowly, the reaction mixture stirred for 1h and 1-phenyl-1H-imidazo[4,5-*b*]pyridine[74] (300 mg, 1.54 mmol) was added as a solution in 3.1 mL of THF. The reaction mixture was stirred for 50 min at which time hexachloroethane (729 mg, 3.08 mmol) was added at -78°C as a solution in 1.7 mL of THF. The reaction mixture was stirred 1 h at -78 °C, warmed to RT over 0.5 h. At this time the reaction was quenched with 2 mL of $NH_4Cl_{(aq)}$, diluted with 10 mL of H_2O and poured into 12 mL of EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 8 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified on a silica gel column (4.5 cm x 12 cm) eluting with 4% MeOH / CH_2Cl to give 219 mg of a brown solid. (63%)

^{1}H NMR: (300 MHz, $CDCl_3$) δ= 8.59 (dd, *J* = 3.9 Hz, 1.8 Hz, 1H), 7.63-7.59 (m, 3H), 7.50 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.45-7.42 (m, 2H), 7.23 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H)

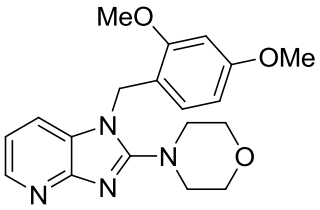
^{13}C NMR: (75.4 MHz, $CDCl_3$) δ= 154.1, 145.8, 143.8, 133.9, 130.2, 129.9, 129.3, 127.2, 119.2, 118.3

FT-IR: (NaCl, thin film) ν = 1610, 1502, 1462, 1415, 1369, 1308, 1109, 777, 700 cm^{-1}.

Anal. Calc. $C_{12}H_8ClN_3$ C, 62.76; H, 3.51; 18.30; found C, 62.49; H, 3.60; N, 18.08

MP: 192-194 ° C

General Procedure E: S_NAr



4-(1-(2,4-dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridin-2-yl)morpholine (50a)

To an oven-dried 25 mL Schlenk tube equipped with a stirbar was added 2-chloro-1-(2,4-dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (**49a**)[77] (100 mg, 0.33 mmol), followed by 0.66 mL of *n*-BuOH, morpholine (35 µL, 0.40 mmol) and $Na_2CO_{3(s)}$ (53 mg, 0.50 mmol). The reaction tube was equipped with a cold-finger condensor and placed in a pre-heated 120 °C oil-bath. After 18h TLC indicated consumption of the chloroazole the reaction mixture was cooled to RT, diluted with 2 mL MeOH, filtered through a Celite plug and concentrated *in vacuo*. The crude material was applied to a silica gel column (2.5 cm x 12 cm), eluting with 3% MeOH / CH_2Cl_2 to give 113 mg of a brown solid. (97%)

^{1}H NMR: (300 MHz, $CDCl_3$) δ= 8.31 (dd, *J* = 5.1 Hz, 1.5 Hz, 1H), 7.20 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 6.92 (dd, *J* = 7.8 Hz, 5.1 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 2.1 Hz, 1H), 6.34 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 5.07 (s, 2H), 3.82-3.75 (m, 10H), 3.34 (t, *J* = 4.8, 4H)

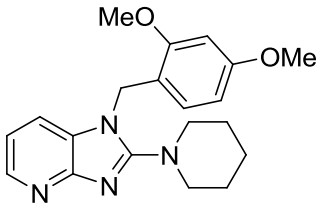
^{13}C NMR: (105.9 MHz, $CDCl_3$) δ= 160.8, 159.7, 157.6, 155.3, 143.5, 128.6, 127.3, 116.4, 116.3, 115.9, 104.3, 98.7, 66.4, 55.5, 55.4, 50.4, 43.4

FT-IR: (NaCl, thin film) ν = 2963, 2852, 1615, 1589, 1510, 1453, 1414, 1370, 1306, 1263, 1157, 1118, 1032, 781 cm^{-1}.

HRMS Calc $(C_{19}H_{22}N_4O_3)Na^+$: 377.1584, Found: 377.1580

MP: 125-128 °C

1-(2,4-dimethoxybenzyl)-2-(piperidin-1-yl)-1H-imidazo[4,5-*b*]pyridine (50b)



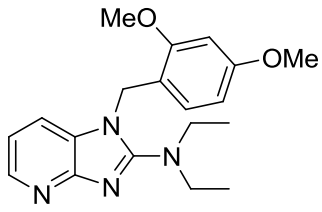
Following general procedure E, 2-chloro-1-(2,4-dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (**49a**) (100mg, 0.33 mmol) was added to an oven-dried 25 mL Schlenk tube, followed by 0.66 mL of *n*-BuOH, piperidine (33 μL, 0.40 mmol) and Na_2CO_3 (53 mg, 0.50 mmol). The reaction tube was equipped with a cold-finger condenser and placed in a pre-heated 120 °C oil-bath. After 18h TLC showed consumption of the chloroazole, the reaction mixture was cooled to RT, diluted with 2 mL of MeOH, filtered through a Celite plug and concentrated *in vacuo*. The crude material was applied to a silica gel column (2.5 cm x 12 cm), eluting with 3% MeOH / CH_2Cl_2 to give 109 mg of a brown oil. (94%)

^{1}H NMR: (300 MHz, $CDCl_3$) δ= 8.25 (dd, *J* = 5.0 Hz, 1.5 Hz, 1H), 7.13 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 6.86 (dd, *J* = 7.8 Hz, 5.0 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 2.3 Hz, 1H), 6.33 (dd, *J* = 8.4 Hz, 2.3 Hz, 1H), 5.03 (s, 2H), 3.81 (s, 3H), 3.75 (s, 3H), 3.28 (app t, *J* = 5.5 Hz, 4H), 1.72 – 1.52 (m, 6H)

^{13}C NMR: (75.4 MHz, $CDCl_3$) δ=160.9, 160.6, 157.6, 155.6, 143.0, 128.7, 127.3, 116.2, 116.2, 115.9, 104.1, 98.6, 55.4, 55.4, 51.2, 43.6, 25.6, 24.3

FT-IR: (NaCl, thin film) ν = 2938, 2850, 1614, 1588, 1528, 1299, 1270, 1208, 1157, 1033, 776, 732 cm^{-1}.

HRMS Calc $(C_{20}H_{24}N_4O_2)Na^+$: 375.1791, Found: 375.1784



1-(2,4-dimethoxybenzyl)-N,N-diethyl-1H-imidazo[4,5-*b*]pyridin-2-amine (50c)

Following general procedure E, 2-chloro-1-(2,4-dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (**49a**) (100 mg, 0.33 mmol) was added to an oven-dried 25 mL sealed tube, followed by 0.66 mL of *n*-BuOH, diethylamine (41 μL, 0.40 mmol) and Na_2CO_3 (53 mg, 0.50 mmol). The reaction tube was sealed and placed in a pre-heated 120 °C oil-bath. After 36h TLC showed consumption of the chloroazole, the reaction mixture was cooled to RT, diluted with 2 mL of MeOH, filtered through a Celite plug and concentrated *in vacuo*. The crude material was applied to a silica gel column (2.5 cm x 12 cm), eluting with 3% MeOH / CH_2Cl_2 to give 115 mg of a brown solid. (85%)

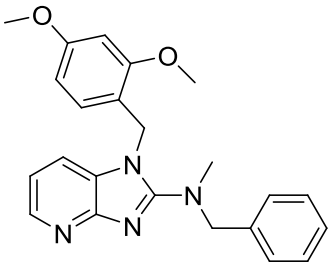
^{1}H NMR: (300 MHz, $CDCl_3$) δ= 8.26 (dd, *J* = 5.0 Hz, 1.5 Hz, 1H), 7.15 (dd, *J* = 7.8 Hz, 1. Hz, 1H), 6.86 (dd, *J* = 7.8 Hz, 5.0 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.48 (d, *J* = 2.3 Hz, 1H), 6.34 (dd, *J* = 8.4 Hz, 2.3 Hz, 1H), 5.05 (s, 2H), 3.38 (s, 3H), 3.76 (s, 3H)

^{13}C NMR: (75.4 MHz, $CDCl_3$) δ= 160.6, 160.1, 157.6, 155.8, 143.0, 128.9, 127.2, 116.4, 115.8, 115.6, 104.1, 98.6, 55.5, 55.5, 45.6, 43.7, 13.2

FT-IR: (NaCl, thin film) ν = 2970, 2936, 1615, 1589, 1509, 1412, 1209, 1157, 1121, 1029, 776 cm^{-1}.

Anal. Calc. $C_{19}H_{24}N_4O_2$ C, 67.04; H, 7.11; N, 16.08; found C, 67.42; H, 7.00; N, 16.08

MP: 115-117 ° C



***N*-benzyl-1-(2,4-dimethoxybenzyl)-N-methyl-1H-imidazo[4,5-*b*]pyridin-2-amine (50d)**

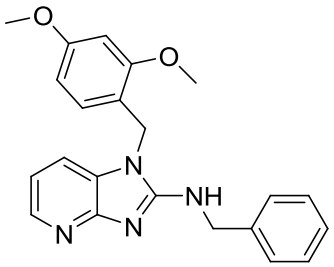
Following general procedure E, 2-chloro-1-(2,4-dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (**49a**) (100 mg, 0.33 mmol) was added to an oven-dried 25 mL Schlenk tube, followed by 0.66 mL of *n*-butanol, N-benzylmethylamine (52 μL, 0.40 mmol) and Na_2CO_3 (53 mg, 0.50 mmol). The reaction tube was equipped with a cold-finger condenser and placed in a pre-heated 120 °C oil-bath. After 18h TLC showed consumption of the chloroazole, the reaction mixture was cooled to RT, diluted with 2 mL of MeOH, filtered through a Celite plug and concentrated *in vacuo*. The crude material was applied to a silica gel column (2.5 cm x 12 cm), eluting with 3% MeOH / CH_2Cl_2 to give 115 mg of a brown oil. (90%)

^{1}H NMR: (300 MHz, $CDCl_3$) δ= 8.26 (dd, *J* = 5.0 Hz, 1.1 Hz, 1H), 7.32 – 7.18 (m, 5H), 7.16 (dd, *J* = 7.8 Hz, 1.3 Hz, 1H), 6.88 (dd, *J* = 7.8 Hz, 5.0 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.41 (d, *J* = 2.2 Hz, 1H), 6.32 (dd, *J* = 8.4 Hz, 2.3 Hz, 1H), 5.08 (s, 2H), 4.48 (s, 2H), 3.73 (s, 3H), 3.66 (s, 3H), 2.94 (s, 3H)

^{13}C NMR: (75.4 MHz, $CDCl_3$) δ= 160.8, 160.5, 157.4, 155.4, 143.0, 137.2, 129.1, 128.5, 127.6, 127.4, 127.1, 116.1, 115.9, 115.7, 104.1, 98.5, 57.4, 55.4, 55.2, 43.7, 39.1

FT-IR: (NaCl, thin film) ν = 2950, 2850, 1614, 1590, 1540, 1453, 1413, 1303, 1269, 1209, 1157, 1033, 777, 734 cm^{-1}.

HRMS Calc $(C_{23}H_{24}N_4O_2)Na^+$: 411.1791, Found: 411.1782



***N*-benzyl-1-(2,4-dimethoxybenzyl)-1*H*-imidazo[4,5-*b*]pyridine-2-amine (50e)**

Following general procedure E, 2-chloro-1-(2,4-dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (**49a**) (100 mg, 0.33 mmol) in a solution of 0.66 mL of *n*-butanol, benzylamine (44 μL, 0.40 mmol), and sodium carbonate (53 mg, 0.50 mmol) were added, immersed in a 120°C pre-heated oil-bath for 16h, allowed to cool to rt over 0.5 h, diluted with 2 mL of MeOH, filtered through a Celite plug, and concentrated *in vacuo*. The crude product was purified on a silica gel column (2.5 cm x 12 cm) eluting with 4% MeOH / CH_2Cl to give 105 mg of an off white solid. (85%)

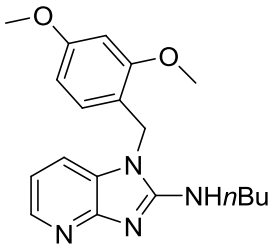
^{1}H NMR: (300 MHz, $CDCl_3$) δ=8.22 (dd, *J* = 5.1 Hz, 1.2 Hz, 1H), 7.45 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.36-7.32 (m, 5H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.95 (dd, *J* =7 .8 Hz, 5.4 Hz, 1H), 9.66 (dd, *J* = 8.1 Hz, 2.4 Hz, 1H), 6.38 (d, *J* = 2.4, 1H), 5.66 (br s, 1H), 4.96 (s, 2H), 4.75 (d, *J*= 5.4, 2H), 3.78 (s, 3H), 3.46 (s, 3H)

^{13}C NMR: (75.4 MHz, $CDCl_3$) δ= 161.3, 157.5, 156.4, 156.1, 142.1, 138.7, 130.9, 128.8, 128.4, 127.8, 127.7, 115.7, 114.6, 113.7, 105.1, 98.9, 55.8, 55.2, 47.6, 40.6

FT-IR: (NaCl, thin film) ν = 3250, 2937, 1617, 1565, 1509, 1454, 1419, 1356, 1266, 1209, 1157, 1031

Anal. Calc. $C_{22}H_{22}N_4O_2$ C, 70.57; H, 5.92; N, 14.96; found C, 70.25; H, 6.21; N, 15.07

MP: 85-88 °C



N-butyl-1-(2,4-dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridin-2-amine (50f)

Following general procedure E, 2-chloro-1-(2,4-dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (**49a**) (100 mg, 0.33 mmol) was added to an oven-dried 25 mL Schlenk tube, followed by 0.66 mL of *n*-BuOH, *n*-butyl amine (39 μL, 0.40 mmol) and Na_2CO_3 (53 mg, 0.50 mmol). The reaction tube was equipped with a cold-finger condenser and placed in a pre-heated 120 °C oil-bath. After 18h TLC showed consumption of the chloroazole, the reaction mixture was cooled to RT, diluted with 2 mL of MeOH, filtered through a Celite plug and concentrated *in vacuo*. The crude material was applied to a silica gel column (2.5 cm x 12 cm), eluting with 3% MeOH / CH_2Cl_2 to give 107 mg of a light brown solid. (96%)

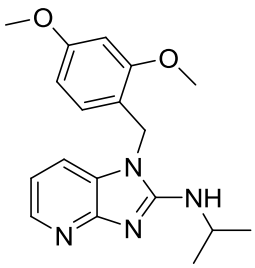
^{1}H NMR: (300 MHz, $CDCl_3$) δ= 8.08 (dd, *J* = 5.1 Hz, 1.4 Hz, 1H), 7.28 (dd, *J* = 7.7 Hz, 1.4 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.82 (dd, *J* = 7.7 Hz, 5.1 Hz, 1H), 6.43 (d, *J* = 2.3 Hz, 1H), 6.38 (dd, *J* = 8.3 Hz, 2.3 Hz, 1H), 5.33 (t, *J* = 5.0 Hz, 1H), 4.90 (s, 2H), 3.80 (s, 3H), 3.73 (s, 3H), 3.49 (app q, *J* = 7.0 Hz, 2H), 1.58 (pent, *J* = 7.2 Hz, 2H), 1.32 (sex, *J* = 7.4 Hz, 2H), 0.88 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR: (75.4 MHz, $CDCl_3$) δ= 161.1, 157.6, 156.3, 141.5, 130.2, 127.6, 115.6, 114.3, 113.5, 104.9, 98.8, 55.5, 55.4, 43.0, 40.5, 31.8, 20.0, 13.8

FT-IR: (NaCl, thin film) ν = 2958, 1612, 1562, 1509, 1458, 1419, 1266, 1209, 1157, 1123, 1036, 771 cm^{-1}.

Anal. Calc. $C_{19}H_{24}N_4O_2$ C, 67.04; H, 7.11; N, 16.46; found C, 66.89; H, 7.55; N, 16.18

MP: 91 – 93 °C



1-(2,4-dimethoxybenzyl)-N-isopropyl-1H-imidazo[4,5-*b*]pyridin-2-amine (50g)

Following general procedure E, 2-chloro-1-(2,4-dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (**49a**) (100 mg, 0.33 mmol) was added to an oven-dried 25 mL sealed tube, followed by 0.66 mL of *n*-BuOH, isopropylamine (34 μL, 0.40 mmol) and Na_2CO_3 (53 mg, 0.50 mmol). The reaction tube was equipped with a cold-finger condenser and placed in a pre-heated 120 °C oil-bath. After 36h TLC showed consumption of the chloroazole, the reaction mixture was cooled to RT, diluted with 2 mL of MeOH, filtered through a Celite plug and concentrated *in vacuo*. The crude material was applied to a silica gel column (2.5 cm x 12 cm), eluting with 3% MeOH / CH_2Cl_2 to give 98 mg of a brown solid. (92%)

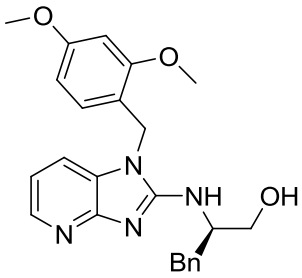
^{1}H NMR: (300 MHz, $CDCl_3$) δ= 8.11 (dd, *J* = 5.1 Hz, 1.5 Hz, 1H), 7.32 (dd, *J* = 7.1 Hz, 1.5 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.84 (dd, *J* = 7.7 Hz, 5.1 Hz, 1H), 6.45 (d, *J* = 2.3 Hz, 1H), 6.41 (dd, *J* = 8.3 Hz, 2.4 Hz, 1H), 5.14 (br d, *J* = 7.3 Hz, 1H), 4.90 (s, 2H), 4.24 (oct, *J* = 6.5 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 1.25 (d, *J* = 6.5 Hz, 6H)

^{13}C NMR: (75.4 MHz, $CDCl_3$) δ= 161.4, 157.7, 156.5, 155.7, 141.6, 130.7, 127.7, 115.8, 114.3, 113.6, 105.1, 99.0, 55.6, 55.6, 45.0, 40.7, 23.4

FT-IR: (NaCl, thin film) ν = 2968, 1600, 1559, 1508, 1419, 1265, 1208, 1157, 1130, 1034, 913, 769, 732 cm^{-1}.

Anal. Calc. $C_{18}H_{22}N_4O_2$ C, 66.24; H, 6.79; N, 17.17; found C, 66.35; H, 6.94; N, 16.91

MP: 85 – 87 °C



(R)-2-(1-(2,4-dimethoxybenzyl)-1H-imidazo[4,5-*b*]166yridine-2-ylamino)-3-phenylpropan-1-ol (50i)

Following general procedure E, 2-chloro-1-(2,4-dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (**49a**) (100mg, 0.33 mmol) was added to an oven-dried 25 mL Schlenk tube, followed by 0.66 mL of *n*-BuOH, D-phenylalaninol (61 mg , 0.40 mmol) and Na_2CO_3 (53 mg, 0.50 mmol). The reaction tube was equipped with a cold-finger condenser and placed in a pre-heated 120 °C oil-bath. After 18h TLC showed consumption of the chloroazole, the reaction mixture was cooled to RT, diluted with 2 mL of MeOH, filtered through a Celite plug and concentrated *in vacuo*. The crude material was applied to a silica gel column (2.5 cm x 12 cm), eluting with 3% MeOH / CH_2Cl_2 to give 70 mg of a brown oil. (51%)

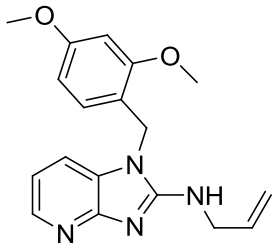
^{1}H NMR: (300 MHz, $CDCl_3$) δ= 8.07 (dd, *J* = 5.1 Hz, 1.4 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.20 – 7.10 (m, 5H), 6.89 (d, *J* = 9.0 Hz, 1H), 6.83 (dd, *J* = 7.7 Hz, 5.2 Hz, 1H), 6.37 – 6.30 (m, 2H), 4.78 (AB d, 16.2 Hz, 2H), 4.36 (br t, *J* = 4.8 Hz, 1H), 3.90 (dd, *J* = 11.4 Hz, 3.7 Hz, 1H), 3.79 – 3.70 (m, 4H), 3.64 (s, 3H), 3.03 (d, *J* = 6.9 Hz, 2H)

^{13}C NMR: (75.4 MHz, $CDCl_3$) δ= 161.2, 157.8, 156.3, 155.1, 140.6, 138.2, 130.4, 129.5, 128.5, 128.0, 126.4, 115.3, 114.6, 114.6, 104.8, 98.9, 64.3, 56.8, 55.5, 55.5, 41.1, 37.4

FT-IR: (NaCl, thin film) ν = 2669 (br), 1609, 1561, 1509, 1458, 1421, 1290, 1266, 1209, 1157, 1037, 912, 742 cm^{-1}.

HRMS Calc $(C_{24}H_{26}N_4O_3)Na^+$: 441.1897, Found: 441.1893

$[\alpha]_D$ = 26.5° (0.33, MeOH)



N-allyl-1-(2,4-dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridin-2-amine (50j)

Following general procedure E, 2-chloro-1-(2,4-dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (**49a**) (100mg, 0.33 mmol) was added to an oven-dried 25 mL Schlenk tube, followed by 0.66 mL of *n*-BuOH, allyl amine (30 μL, 0.40 mmol) and Na_2CO_3 (53 mg, 0.50 mmol). The reaction tube was equipped with a cold-finger condenser and placed in a pre-heated 120 °C oil-bath. After 18 h TLC showed consumption of the chloroazole, the reaction mixture was cooled to RT, diluted with 2 mL of MeOH, filtered through a Celite plug and concentrated *in vacuo*. The crude material was applied to a silica gel column (2.5 cm x 12 cm), eluting with 3% MeOH / CH_2Cl_2 to give 70 mg of a pale-brown solid. (72%)

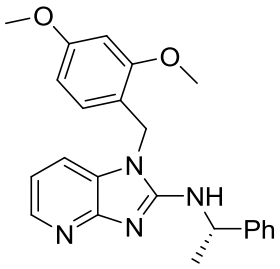
^{1}H NMR: (300 MHz, $CDCl_3$) δ= 8.17 (dd, *J* = 5.1 Hz, 1.5 Hz, 1H), 7.34 (dd, *J* = 7.5 Hz, 1.2 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 6.86 (dd, *J* = 7.5 Hz, 5.1 Hz, 1H), 6.47-6.38 (m, 2H), 6.08-5.93 (m, 1H), 5.38 (br t, *J* = 5.4 Hz, 1H), 5.26-5.10 (m, 2H), 4.96 (s, 2H), 4.19 (t, *J* = 5.4 Hz, 2H), 3.81 (s, 3H), 3.77 (s, 3H)

^{13}C NMR: (75.4 MHz, $CDCl_3$) δ= 161.3, 157.6, 156.5, 156.1, 142.0, 135.0, 130.6, 127.7, 116.6, 115.8, 114.5, 113.7, 105.0, 99.0, 55.6, 45.9, 40.8

FT-IR: (NaCl, thin film) ν = 2917, 2849, 1610, 1561, 1509, 1459, 1420, 1289, 1266, 1130, 1035, 772 cm^{-1}.

Anal. Calc. $C_{18}H_{20}N_4O_2$ C, 66.65; H, 6.21; N, 17.27; found C, 66.26; H, 6.58; N, 17.03

MP: 86 – 88 °C



(S)-1-(2,4-dimethoxybenzyl)-N-(1-phenylethyl)-1H-imidazo[4,5-*b*]pyridin-2-amine (50k)

Following general procedure E, 2-chloro-1-(2,4-dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (**49a**) (100mg, 0.33 mmol) was added to an oven-dried 25 mL Schlenk tube, followed by 0.66 mL of *n*-BuOH, (S)-1-phenylethylamine (49 μL, 0.40 mmol) and Na_2CO_3 (53 mg, 0.50 mmol). The reaction tube was equipped with a cold-finger condenser and placed in a pre-heated 120 °C oil-bath. After 24 h TLC showed consumption of the chloroazole, the reaction mixture was cooled to RT, diluted with 2 mL of MeOH, filtered through a Celite plug and concentrated *in vacuo*. The crude material was applied to a silica gel column (2.5 cm x 12 cm), eluting with 3% MeOH / CH_2Cl_2 to give 80 mg of a while solid. (62%)

^{1}H NMR: (300 MHz, $CDCl_3$) δ= 8.14 (dd, *J* = 5.1 Hz, 1.4 Hz, 1H), 7.40 – 7.19 (m, 6H), 7.10 (d, *J* = 8.1 Hz, 1H), 6.86 (dd, *J* = 7.7 Hz, 5.1 Hz, 1H), 6.45 – 6.35 (m, 2H), 5.62 (d, *J* = 6.9, Hz, 1H), 5.34 (pent, *J* = 6.7 Hz, 1H), 4.93 (AB d, *J* = 16.0 Hz, 2H), 3.76 (s, 3H), 3.54 (s, 3H), 1.61 (d, *J* = 6.8 Hz, 3H)

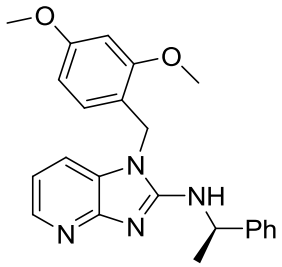
^{13}C NMR: (75.4 MHz, $CDCl_3$) δ= 161.2, 157.5, 156.5, 155.4, 143.8, 141.9, 130.9, 128.6, 127.5, 127.4, 126.5, 115.7, 114.4, 113.6, 105.0, 98.8, 55.5, 55.2, 52.3, 40.6, 22.2

FT-IR: (NaCl, thin film) ν = 2971, 2935, 1597, 1558, 1509, 1418, 1209, 1127, 1033, 701 cm^{-1}.

HRMS Calc $(C_{23}H_{24}N_4O_2)Na^+$: 411.1791, Found: 411.1787

MP: 121-122 °C

$[\alpha]_D$ = 41.0° (0.55, MeOH)



(*R*)-1-(2,4-dimethoxybenzyl)-N-(1-phenylethyl)-1H-imidazo[4,5-*b*]pyridin-2-amine (50l)

Following general procedure E, 2-chloro-1-(2,4-dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (**49a**) (100 mg, 0.33 mmol) was added to an oven-dried 25 mL Schlenk tube, followed by 0.66 mL of *n*-BuOH, (*R*)-1-phenylethylamine (49 μL, 0.40 mmol) and Na_2CO_3 (53 mg, 0.50 mmol). The reaction tube was equipped with a cold-finger condenser and placed in a pre-heated 120 °C oil-bath. After 24 h TLC showed consumption of the chloroazole, the reaction mixture was cooled to RT, diluted with 2 mL of MeOH, filtered through a Celite plug and concentrated *in vacuo*. The crude material was applied to a silica gel column (2.5 cm x 12 cm), eluting with 3% MeOH / CH_2Cl_2 to give 83 mg of a brown oil. (65%)

^{1}H NMR: (300 MHz, $CDCl_3$) δ= 8.11 (dd, *J* = 5.1 Hz, 1.3 Hz, 1H), 7.40 – 7.19 (m, 6H), 7.08 (d, *J* = 8.1 Hz, 1H), 6.84 (dd, *J* = 7.7 Hz, 5.1 Hz, 1H), 6.43 – 6.36 (m, 2H), 5.72 (d, *J* = 7.0, Hz, 1H), 5.30 (pent, *J* = 6.8 Hz, 1H), 4.91 (AB d, *J* = 16.1 Hz, 2H), 3.74 (s, 3H), 3.53 (s, 3H), 1.59 (d, *J* = 6.8 Hz, 3H)

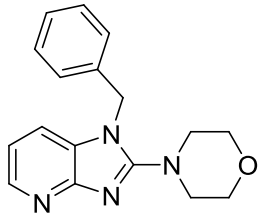
^{13}C NMR: (75.4 MHz, $CDCl_3$) δ= 161.2, 157.4, 156.4, 155.4, 143.8, 141.8, 130.9, 128.6, 127.5, 127.4, 126.5, 115.7, 114.3, 113.5, 105.0, 98.9, 55.5, 55.2, 52.3, 40.5, 22.2

FT-IR: (NaCl, thin film) ν = 2970, 2934, 1599, 1508, 1419, 1266, 1208, 1033, 700 cm^{-1}.

HRMS Calc $(C_{23}H_{24}N_4O_2)Na^+$: 411.1791, Found: 411.1787

MP: 122-123 °C

$[\alpha]_D$ = -39.2° (0.71, MeOH)



4-(1-benzyl-1*H*-imidazo[4,5-*b*]pyridine-2-yl)morpholine (51)

Following general procedure E, 1-benzyl-2-chloro-1*H*-imidazo[4,5-*b*]pyridine (**49b**) (81 mg, 0.33 mmol), 0.66 mL of *n*-BuOH, morpholine (34 μL, 0.40 mmol) and sodium carbonate (53 mg, 0.50 mmol) were added, immersed in a 120°C pre-heated oil-bath for 16h, allowed to cool to rt over 0.5 h, diluted with 2 mL of MeOH, filtered through a Celite plug, and concentrated *in vacuo*. The crude product was purified on a silica gel column (2.5 cm x 12 cm) eluting with 4% MeOH in CH_2Cl to give 84 mg of a yellow-white solid. (88%)

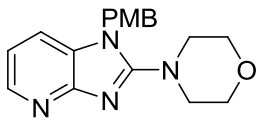
^{1}H NMR: (300 MHz, $CDCl_3$) δ= 8.34 (dd, *J* = 5.1 Hz, 1.5 Hz, 1H), 7.34- 7.30 (m, 3H) 7.13-7.10 (m, 2H), 6.94 (dd, *J* = 7.8 Hz, 5.1 Hz, 1H), 5.21 (s, 2H), 3.78 (t, *J* = 4.5 Hz, 4H), 3.34 (t, 4.8, 4H)

^{13}C NMR: (75.4 MHz, $CDCl_3$) δ=159.6, 155.1, 143.7, 135.3, 129.3, 128.5, 128.1, 125.9, 116.6, 116.6, 66.3, 50.6, 48.1

FT-IR: (NaCl, thin film) ν =2964, 2917, 2855, 1624, 1584, 1527, 1451, 1414, 1368, 1274, 1116, 1007, 855, 779, 734, 698

HRMS Calc $(C_{17}H_{18}N_4O)Na^+$: 317.1372, Found: 317.1372

MP: 123- 125.5 ° C

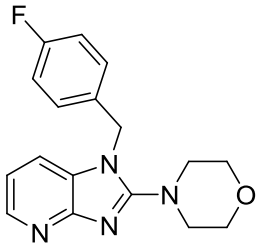


4-(1-(4-Methoxybenzyl)-1H-imidazo[4,5-*b*]pyridin-2-yl)morpholine52)[74]

Following general procedure E, 0.66 mL of *n*-BuOH, 2-chloro-1-(4-methoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (**49c**) (90 mg, 0.33 mmol), sodium carbonate (52 mg, 0.495 mmol), and morpholine (0.034 mL, 0.396 mmol) were added to a 25 mL Schlenk tube. The reaction mixture was stirred overnight at which time TLC showed consumption of the starting material. The reaction mixture was warmed to room temperature, diluted with 2 mL of MeOH, filtered through Celite and concentrated *in vacuo*. The crude product was purified on a silica column (2.5 cm x 12 cm) eluting with 4% MeOH/ CH_2Cl_2 to give 79 mg as a gold solid. (74%)

^{1}H NMR (300MHz, $CDCl_3$) δ= 8.32 (dd, *J* = 5.1 Hz, 1.5 Hz, 1H), 7.19 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.03 (d, *J* = 9 Hz, 2H), 6.93 (dd, *J* = 7.8 Hz, 4.8 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.26 (s, 2H), 3.78 (t, *J* = 9.3 Hz, 4H), 3.75 (s, 3H), 3.34 (t, *J* = 9.3 Hz, 4H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ=159.6, 159.33, 155.2, 143.7, 128.4, 127.3, 127.2, 116.5, 114.6, 66.4, 55.36, 50.6, 47.6



4-(1-(4-Fluorobenzyl)-1H-imidazo[4,5-*b*]pyridin-2-yl)morpholine(53)

Following general procedure E, 0.66 mL of *n*-BuOH (0.5M), 2-chloro-1-(4-fluorobenzyl)-1H-imidazo[4,5-*b*]pyridine (**49d**) (88 mg, 0.33 mmol), sodium carbonate (52 mg, 0.50 mmol), and morpholine (34 μL, 0.40 mmol) were added to a 25 mL Schlenk tube. The reaction mixture was stirred overnight and TLC showed consumption of the starting material. The reaction mixture was warmed to room temperature, diluted with 2 mL MeOH, filtered through Celite and concentrated *in vacuo*. The crude product was purified on a silica column (2.5 cm x 12 cm) eluting with 4% MeOH/ CH_2Cl_2 to give 54 mg as a gold solid. (52%)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.35 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 7.19 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.13-6.94 (m, 5H), 5.18 (s, 2H), 3.79 (t, *J* = 9.3 Hz, 4H), 3.34 (t, *J* = 9.6 Hz, 4H)

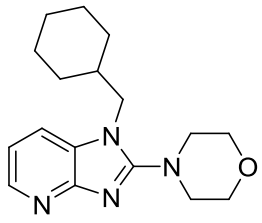
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 162.4 (d, *J* = 247.1 Hz), 159.6, 155.3, 143.9, 131.1 (d, *J* = 3.3 Hz), 128.3, 127.8 (d, *J* = 8.1 Hz), 116.7, 116.3 (d, *J* = 21.7 Hz), 66.4, 50.7, 47.5

^{19}F NMR (282.4 MHz, $CDCl_3$) δ= -114.1— -114.2 (m)

FT-IR (NaCl, thin film) ν = 3004, 2855, 2344, 1718, 1608, 1508, 1411, 1274 cm^{-1}.

Anal. Calc. $C_{17}H_{17}FN_4O$ C, 65.37; H, 5.49; N, 17.94; found C, 65.13; H, 5.83; N, 18.04

MP: 157-159°C



4-(1-(Cyclohexylmethyl)-1H-imidazo[4,5-*b*]pyridin-2-yl)morpholine (54)

Following general procedure E, 0.66 mL of *n*-BuOH, 2-chloro-1-(cyclohexylmethyl)-1H-imidazo[4,5-*b*]pyridine (**49e**) (82 mg, 0.33 mmol), sodium carbonate (52 mg, 0.50 mmol), and morpholine (0.034 mL, 0.40 mmol) were added to a 25 mL Schlenk tube. The reaction mixture was stirred overnight and TLC showed consumption of the starting material. The reaction mixture was warmed to room temperature, diluted with 2 mL MeOH, filtered through Celite and concentrated *in vacuo*. The crude product was purified on a silica column (2.5 cm x 12 cm) eluting with 4% MeOH/ CH_2Cl_2 to give 87 mg as a brown solid. (88%)

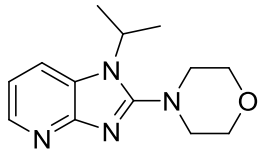
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.29 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H), 7.42 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 6.99 (dd, *J* = 8.1 Hz, 5.1 Hz, 1H), 3.82 (t, *J* = 9 Hz, 4H), 3.78 (s, 2H), 3.32 (t, *J* = 9.3 Hz, 4H), 1.89-1.82 (m, 1H), 1.65-1.58 (m, 3H), 1.44-1.40 (m, 2H), 1.11- 1.01 (m, 3H), 0.97-0.85 (m, 2H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 159.8, 154.9, 143.4, 127.8, 116.8, 116.4, 66.5, 50.7, 50.6, 37.3, 30.8, 26.1, 25.5

FT-IR (NaCl, thin film) ν = 2928, 2366, 2344, 1773, 1637, 1419, 1116 cm^{-1}

HRMS Calc $(C_{17}H_{24}N_4O)Na^+$: 323.1842, Found: 323.1840

MP: 112-117°C



4-(1-isopropyl-1*H*-imidazo[4,5-*b*]pyridine-2-yl)morpholine (55)

Following general procedure E, 2-chloro-1-isopropyl-1*H*-imidazo[4,5-*b*]pyridine (**49f**) (65.2 mg, 0.33 mmol), 0.66 mL of *n*-butanol, morpholine (34 μL, 0.40 mmol)and sodium carbonate (53 mg, 0.50 mmol) were added, immersed in a 120°C pre-heated oil-bath for 16 h, allowed to cool to RT over 0.5 h, diluted with 2 mL of MeOH, filtered through a Celite plug, and concentrated *in vacuo*. The crude product was purified on a silica gel column (2.5 cm x 12 cm) eluting with 4% MeOH / CH_2Cl to give 65 mg of an off white solid. (79%)

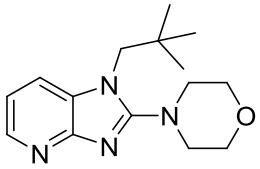
^{1}H NMR: (300 MHz, $CDCl_3$) δ= 8.32 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.61 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 6.99 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 4.63-4.54 (m, 1H), 3.86 (t, *J* = 4.6 Hz, 4H), 3.30 (t, 4.6 Hz, 4H), 1.54 (d, *J* = 6.9 Hz, 6H)

^{13}C NMR: (75.4 MHz, $CDCl_3$) δ= 159.2, 155.5, 143.3, 125.6, 118.5, 116.2, 66.4, 51.4, 48.0, 21.3

FT-IR: (NaCl, thin film) ν= 3250, 2961, 2855, 1520, 1453, 1413, 1372, 1281, 1112, 963, 853, 806, 791 cm^{-1}

HRMS Calc $(C_{13}H_{18}N_4O)Na^+$: 269.1373, Found: 269.1371

MP: 138-141 °C



4-(1-neopentyl-1*H*-imidazo[4,5-*b*]pyridine-2-yl)morpholine (56)

Following general procedure E, 2-chloro-1-neopentyl-1H-imidazo[4,5-*b*]pyridine (**49g**) (74.5 mg, 0.33 mmol), 0.66 mL of *n*-BuOH, morpholine (34 μL, 0.40 mmol) and sodium carbonate (53 mg, 0.50 mmol) were added, immersed in a 120°C pre-heated oil-bath for 16 h, allowed to cool to RT over 0.5 h, diluted with 2 mL of MeOH, filtered through a Celite plug, and concentrated *in vacuo*. The crude product was purified on a silica gel column (2.5 cm x 12 cm) eluting with 4% MeOH / CH_2Cl to give 57 mg of a yellow/white solid. (63%)

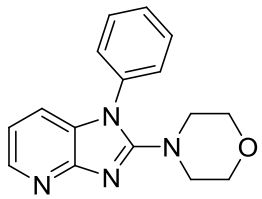
^{1}H NMR: (300 MHz, $CDCl_3$) δ= 8.35 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H), 7.51 (dd, *J* = 8.1 Hz, 4.5 Hz, 1H), 7.05 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H) 3.86-3.82 (m, 6H), 3.27 (t, *J* = 4.5 Hz, 4H), 0.92 (s, 9H)

^{13}C NMR: (75.4 MHz, $CDCl_3$) δ=159.9, 154.3, 143.5, 128.1, 118.1, 116.7, 66.5, 54.8, 51.0, 35.4, 28.8

FT-IR: (NaCl, thin film) ν = 2963, 2856, 1520, 1452, 1413, 1368, 1280, 1116, 977, 784 cm^{-1}

HRMS Calc $(C_{15}H_{22}N_4O)Na^+$: 297.1686, Found: 297.1681

MP: 121-126 °C



4-(1-phenyl-1*H*-imidazo[4,5-*b*]pyridine-2-yl)morpholine (57)

Following general procedure E, 2-chloro-1-phenyl-1H-imidazo[4,5-*b*]pyridine (**49h**) (65 mg, 0.33 mmol), 0.66 mL of *n*-butanol, morpholine (34 μL, 0.40 mmol)and sodium carbonate (53 mg, 0.50 mmol) were added, immersed in a 120 °C pre-heated oil-bath for 16 h, allowed to cool to RT over 0.5 h, diluted with 2 mL of MeOH, filtered through a Celite plug, and concentrated *in vacuo*. The crude product was purified on a silica gel column (2.5 cm x 12 cm) eluting with 4% MeOH in CH_2Cl to give 76 mg of an off white solid. (82%)

^{1}H NMR: (300 MHz, $CDCl_3$) δ= 8.31 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 7.59-7.54 (m, 2H), 7.48-7.43 (m, 3H), 7.27-7.24 (m, 1H), 6.93 (dd, *J* = 8.1 Hz, 5.1 Hz, 1H), 3.65 (t, J = 4.5 Hz, 4H), 3.32 (t, *J* = 4.5 Hz, 4H)

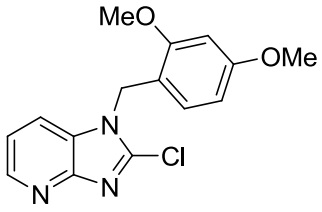
^{13}C NMR: (75.4 MHz, $CDCl_3$) δ= 157.8, 155.1, 143.7, 136.5, 130.4, 129.1, 128.8, 125.8, 116.3, 115.7, 66.2, 48.9

FT-IR: (NaCl, thin film) ν = 1594, 1533, 1496, 1450, 1413, 115, 953, 859, 769, 700 cm^{-1}

HRMS Calc $(C_{16}H_{16}N_4O)Na^+$: 303.1216, Found: 303.1213

MP: 129-132 °C

7.5 TOTAL SYNTHESIS OF PENTOSIDINE



2-chloro-1-(2,4-dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (49a)

To a flame-dried 50 mL round-bottom flask equipped with a stirbar was added 14.9 mL THF and diisopropylamine (1.07 mL, 7.64 mmol). The reaction was cooled to -78 °C (CO_2/acetone) and, *n*-BuLi (3.82 mL, 1.95M in hexanes, 7.46 mmol) was added slowly, the reaction stirred for 1h and 1-(4-methoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (**25c**) (1.0 g, 3.73 mmol) was added as a solution in 7.5 mL THF. The reaction mixture was stirred for 1 h at which time hexachloroethane (1.77 g, 7.46 mmol) was added at -78°C as a solution in 4 mL THF. The reaction was stirred 2 h at -78 °C, warmed to RT and stirred for an additional 0.5 h. At this time the reaction was quenched with 2 mL of $NH_4Cl_{(aq)}$, diluted with 10 mL of H_2O and poured into 20 mL of EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified on a silica gel column (4.5 cm x 12 cm) eluting with 3% MeOH / CH_2Cl_2 to give 920 mg of an oil that solidified to a brown solid when triturated with 5 mL of MeCN. (81%)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.50 (dd, *J* = 4.8 Hz, 1.5 Hz, 1H), 7.59 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 7.14 (dd, *J* = 8.1 Hz, 4.8 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.45 – 6.39 (m, 2H), 5.33 (s, 2H), 3.79 (s, 3H), 3.78 (s, 3H)

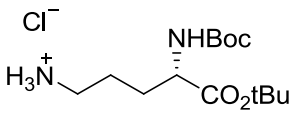
^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 161.2, 158.1, 153.9, 144.9, 144.3, 129.9, 128.0, 118.5, 118.2, 114.8, 104.2, 98.5, 55.4, 55.3, 43.8

FT-IR: (NaCl, thin film) ν = 2939, 2837, 1612, 1589, 1509, 1463, 1410, 1371, 1278, 1210, 1033, 834, 781 cm^{-1}.

HRMS (ESI) Calc ($C_{15}H_{14}ClN_3O_2$)Na+:, 326.0667 Found: 326.0671

MP: 92 – 93 °C

R_f (4% MeOH / CH_2Cl_2): 0.24

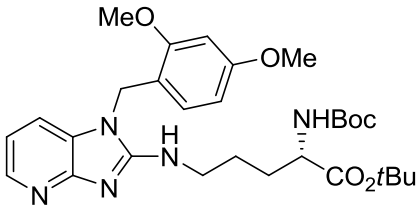


Boc-Orn(H)-O*t*Bu-HCl (83)[209,210]

To a flame-dried 100mL RBF equipped with a stirbar was added 20 mL CH_2Cl_2 and 20 mL *t*-BuOH followed by Boc-Orn(Z)-OH (3.66 g, 10 mmol). N,N'-diisopropyl-*t*-butylisourea (12 mL, 50 mmol) was added and the reaction was placed in a 50 °C pre-heated oil-bath. A precipitate quickly formed, and the reaction was stirred for 24h then cooled to RT. The reaction was filtered through a Celite plug and concentrated *in vacuo*. The crude product was passed through a silica gel plug (150 mL coarse fritted funnel) to remove diisopropyl urea, eluting with 30% EtOAc / hexanes to give Boc-Orn(Z)-O*t*Bu in quantitative yield. This material was taken on without further purification.

The Boc-Orn(Z)-O*t*Bu prepared above was dissolved in 38 mL EtOH and added to a 100 mL RBF equipped with a stirbar. 1N $HCl_{(aq)}$ (11 mL) was added followed by 5 % palladium on carbon (717 mg). H_2(g) was bubbled through the reaction for 5 min before a H_2(g) balloon was equipped. The reaction mixture was stirred for 24h at which point TLC analysis indicated consumption of the Cbz protected amine. The reaction was filtered through a Celite plug eluting with EtOH. The filtrate was concentrated *in vacuo*, giving a sticky oil, which was triturated with methyl *tert*-butyl ether (50 mL), and concentrated *in vacuo* to give **83** as a white fluffy solid (3.2 g, 98%).

^{1}H NMR (300 MHz, CD_3OD) δ= 3.97 (m, 1H), 2.94 (t, *J* = 7.2, 2H), 1.92 – 1.65 (m, 4H), 1.48 (s, 9H), 1.45 (s, 9H).



(S)-*tert*-butyl 2-(tert-butoxycarbonylamino)-5-(1-(2,4-dimethoxybenzyl)-1H-imidazo[4,5-*b*]pyridin-2-ylamino)pentanoate (82)

To an oven-dried 50 mL Schlenk tube equipped with a stirbar was sequentially added Boc-Orn(H)-O*t*Bu·HCl **83** (2.14 g, 6.58 mmol) followed by chloro-azole **49a** (1.0 g, 3.29 mmol) and 6.6 mL *n*-BuOH. Diisopropylethylamine (2.87 mL, 16.45 mmol) was added and the reaction vessel was then equipped with a cold-finger under a positive pressure of $Ar_{(g)}$ and immersed in a 120°C pre-heated oil-bath. After 18 h TLC analysis indicated complete consumption of chloro-azole **83**. The reaction mixture was cooled to RT, diluted with 15 mL of EtOAc and, concentrated *in vacuo* to give a purple semi-solid which was purified on a silica gel column, eluted with 4% MeOH / CH_2Cl_2 to give a 3:1 mixture of the desired product with cyclized Orn **88**. The product was further purified on a silica gel column eluted with 3% EtOH / CH_2Cl_2 to give 1.6 g of **82** as a yellow solid (87%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.18 (dd, *J* = 5.1 Hz, 1.5 Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 8.1 Hz, 1H), 6.87 (dd, *J* = 7.8 Hz, 5.1 Hz, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.42 (dd, *J* = 8.4 Hz, 2.1 Hz, 1H), 5.34 (brs, 1H), 5.13 (brd, *J* = 8.1 Hz, 1H), 4.96 (s, 2H), 4.22 – 4.05 (m, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.66 – 3.55 (m, 2H), 1.90 – 1.60 (m, 4H), 1.43 (s, 9H), 1.41 (s, 9H)

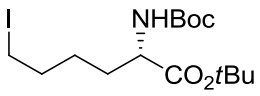
^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 171.8, 161.2, 157.7, 156.5, 156.2, 142.0, 130.0, 127.6, 115.7, 114.4, 113.6, 104.9, 99.0, 82.1, 79.8, 55.7, 55.5, 53.7, 43.0, 40.7, 30.8, 28.4, 28.0, 25.6, 22.6

FT-IR: (NaCl, thin film) ν = 2977, 2935, 1710, 1612, 1561, 1509, 1420, 1366, 1265, 1155, 1042, 772 cm^{-1}.

HRMS (ESI) Calc ($C_{29}H_{41}N_5O_6$)Na+: 578.2949, Found: 578.2958

MP: 69 – 74 °C

R_f (4% MeOH / CH_2Cl_2): 0.23

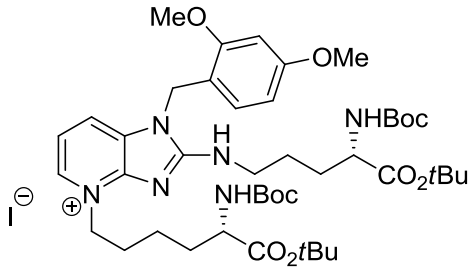


(S)-*tert*-butyl 2-(tert-butoxycarbonylamino)-6-iodohexanoate (63)[160]

To a flame-dried 50 mL RBF equipped with a stirbar was added alcohol **86**[160] (470 mg, 1.55 mmol) in 15.5 mL benzene, followed by imidazole (264 mg, 3.87 mmol), triphenylphosphine (1.02 g, 3.87 mmol) and iodine (787 mg, 3.1 mmol). After 0.5 h the alcohol was judged to be consumed by TLC analysis and the reaction was quenched by the addition of 5 mL saturated aqueous sodium thiosulfate solution. The layers were separated, and the organic layer washed with saturated aqueous sodium thiosulfate solution (2 x 20 mL), water (20 mL) and brine (20 mL). The reaction was then dried over sodium sulfate, concentrated *in vacuo* and purified on a silica gel column (2.5 cm x 12 cm) eluting with 5% EtOAc / hexanes to give 583 mg of a colorless oil (91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 5.05 (br d, *J* = 7.8 Hz, 1H), 4.14 (q, *J* = 6.6 Hz, 1H), 3.15 (t, *J* = 6.9 Hz, 1.93 – 1.45 (s, 9H), 1.41 (s, 9H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 171.8, 155.4, 82.0, 79.7, 55.7, 32.9, 31.9, 28.4, 28.1, 26.0, 6.6



Protected Pentosidine (89)

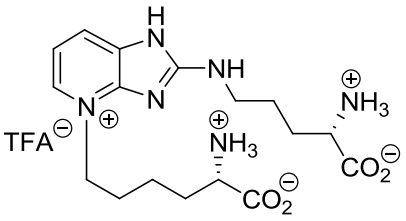
To an oven-dried 25 mL Schlenk tube equipped with a stirbar was added **82** (250 mg, 0.45 mmol) as a solution in 1.25 mL THF followed by iodide **63** (205 mg, 0.50 mmol) which was added as a solution in 1 mL THF. The reaction vessel was then equipped with a cold-finger condenser under a positive pressure of $Ar_{(g)}$ and immersed in a 75 °C pre-heated oil-bath. The reaction was stirred for 72 h at which time TLC showed consumption of **82**. The reaction was cooled to RT, diluted with 3 mL CH_2Cl_2 and concentrated *in vacuo* to give 390 mg of a brown solid. The crude product was purified on a silica gel column (4.5 cm x 12 cm) eluting with 5% MeOH / CH_2Cl_2 to give 300 mg of a pale yellow semi-solid (69%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.15 – 7.85 (m, 2H), 7.61 (d, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.30 (d, *J* = 8.1 Hz, 1H), 6.26 (s, 1H), 5.31 (br s, 2H), 5.15 (br d, *J* = 7.5 Hz, 1H), 5.08 (br d, *J* = 6.9 Hz, 1H), 4.44 (br s, 2H), 4.10 – 3.90 (m, 2H), 3.73 – 3.45 (m, 2H), 3.65 (s, 3H), 3.62 (s, 3H), 2.00 – 1.32 (m, 10 H), 1.27 (br s, 36H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 171.4, 171.3, 161.2, 158.9, 157.9, 155.3, 155.2, 151.0, 132.6, 131.7, 131.2, 118.5, 114.4, 113.8, 104.6, 98.4, 81.6, 79.3, 55.5, 55.2, 53.4, 52.6, 42.7, 42.5, 41.5, 31.9, 29.7, 28.6, 28.0, 27.7, 25.2, 22.0

FT-IR: (NaCl, thin film) ν = 2959, 1586, 1507, 1463, 1296, 1203, 1157, 1114, 1037, 814 cm^{-1}.

HRMS (ESI) Calc ($C_{44}H_{69}N_6IO_{10}$)Na+: 991.4035, Found: 991.4035



Pentosidine (18)[154]

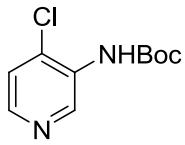
To an oven-dried 25 mL Schlenk tube equipped with a stirbar was added protected pentosidine (**89**) (242 mg, 0.25 mmol) as a solution in 2.25 mL TFA & 0.25 mL H_2O. The reaction mixture was equipped with a cold-finger condenser and placed in a 75°C pre-heated oil-bath for 48 h. The reaction mixture was then cooled to RT and concentrated *in vacuo*. The crude product was partitioned between H_2O (2 mL) and CH_2Cl_2 (2 mL). The layers were separated and the aqueous layer was washed with CH_2Cl_2 (2 x 2 mL) and concentrated *in vacuo* to give a clear brown oil. This oil was dissolved in H_2O (2 mL) and applied to a C18 silica-gel plug, eluting with H_2O. The eluent was concentrated *in vacuo* to give 112 mg of a white solid. (91%)

^{1}H NMR (300 MHz, D_2O) δ= 8.69 (br s, 1H, NH) 7.93 (d, *J* = 6 Hz, 1H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.49 (brs, 1H), 7.20 (t, *J* = 6.6 Hz, 1H), 4.51 (t, *J* = 6.3 Hz, 2H), 3.81, (m, 1H), 3.73 (m, 1H), 3.54 (m, 2H), 2.12 – 1.65 (m, 8H), 1.60 – 1.30 (m, 2H)

^{13}C NMR (150.9 MHz, D_2O) δ = 174.6, 174.5, 162.9 (q, J_{C-F} = 36.2), 159.6, 151.5, 132.1, 131.7, 119.6, 116.4 (q, J_{C-F} = 291 Hz), 115.2, 54.6, 54.5, 53.2, 42.1, 30.0, 28.3, 27.8, 24.6, 21.5

α_D^{23} λ 589 nm (c = 0.3, MeOH): 15.9°

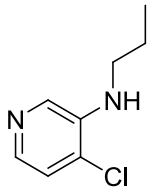
7.6 IMIDAZO[4,5-*C*]PYRIDINES



***tert*-Butyl 4-chloropyridin-3-ylcarbamate (92)**[211, 212]

To a flame-dried 1 L three-neck round-bottom flask equipped with a stirbar, internal temperature probe, and a gas-inlet adaptor was added tert-butyl pyridin-3-ylcarbamate (**91**)[213] (10.0 g, 51.5 mmol) and 258 mL Et_2O (0.2 M). TMEDA (18.5 mL, 123.6 mmol) was then added and the reaction cooled to -78 °C in a CO_2 / acetone bath. *n*-BuLi (55.7 mL, 2.22 M in hexanes, 124 mmol) was added slowly over 20 min, and the reaction mixture was allowed to warm to -10 °C. The reaction was then stirred at -20 °C – -10°C for 2 hours; and then returned to -78 °C. Hexachloroethane (17.1 g, 72.1 mmol) was added as a solution in 72 mL Et_2O (1 M) via addition funnel over 20 min, and the reaction mixture was allowed to warm to room temperature overnight. Upon consumption of the starting material as indicated by TLC the reaction was quenched with saturated $NH_4Cl_{(aq)}$ (250 mL) and diluted with EtOAc (200 mL). The layers were separated, and the organic washing with 0.1 M $HCl_{(aq)}$ (200 mL), followed by brine (250 mL). The organic layer was then dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified on a silica gel column (6 cm x 15 cm) eluting with 30% EtOAc / hexanes to give 7.7 g of a light brown solid. (65%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 9.36 (s, 1H), 8.20 (d, *J* = 5.4 Hz, 1H), 7.28 (d, *J* = 5.1 Hz, 1H), 6.83 (br s, 1H), 1.55 (s, 9H)



4-chloro-N-propylpyridin-3-amine (94g)

To an oven-dried 100 mL round-bottom flask equipped with a stirbar was added 3-amino-4-chloropyridine (2.0 g, 15.56 mmol), EtOAc (24 mL), propionaldehyde (1.23 mL, 17.1 mmol) and trifluoroacetic acid (2.31 mL, 31.1 mmol). The reaction mixture was stirred for 5 min at which time sodium triacetoxyborohydride (3.95 g, 18.7 mmol) was added in three portions over 2 min. The reaction mixture was stirred for 15 min, at which time TLC indicated consumption of the starting material. The reaction mixture was poured into 100 mL saturated $NaHCO_{3(aq)}$ and diluted with EtOAc (25 mL). The layers were separated and the aqueuous layer was extracted with EtOAc (25 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a yellow oil which was purified on a silica gel column (2.5 cm x 12 cm) eluting with 30% EtOAc / hexanes to give 2.05 g of **94g** as a yellow oil. (77%)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.01 (s, 1H), 7.84 (d, *J* = 5.1 Hz, 1H), 7.15 (d, *J* = 5.1 Hz, 1H), 4.18 (br s, 1H), 3.19 (m, 2H), 1.69 (sext, *J* = 7.5 Hz, 2H), 1.02 (t, *J* = 7.5 Hz, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 140.7, 138.3, 133.4, 127.4, 123.8, 45.2, 22.6, 11.6

FT-IR: (NaCl, thin film) ν = 2992, 2938, 1543, 1471, 973, 855, 691 cm^{-1}.

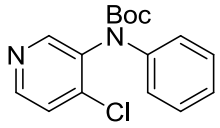
EA: Calculated: $C_8H_{11}ClN_2$, C; 56.31; H, 6.50; N, 16.42; found C, 56.66; H, 6.39; N, 16.65

General Procedure F: Copper Coupling

To an oven-dried Schlenk tube equipped with a stirbar was added copper (I) iodide (10 mol %), potassium phosphate (2 eq.) and tert-butyl 4-chloropyridin-3-ylcarbamate (1 eq). The reaction tube was evacuated and refilled with $Ar_{(g)}$. *trans*-1,2-diaminocyclohexane (**L2**) (20 mol%) was added, followed by 1,4-dioxane (0.5 M), and the haloarene (1.1 eq). The reaction mixture was degassed with three vacuum / $Ar_{(g)}$ purge cycles, equipped with a cold-finger condenser and placed in a pre-heated 110 °C oil-bath. The reaction is stirred overnight, cooled to RT and diluted with EtOAc. The reaction mixture was then filtered through a Celite plug, concentrated *in vacuo* and purified by silica gel column chromatography using the indicated solvent system to give the desired product.

General Procedure G: Deprotection

To an oven-dried round-bottom flask equipped with a stirbar was added the Boc-protected compound (1 eq) followed by dichloromethane (0.5 M). The reaction was cooled to 0 °C and trifluoroacetic acid (0.17 M) was added. The reaction mixture was allowed to warm to RT and stirred overnight until TLC indicated consumption of the starting material. The reaction was then poured into sat. $NaHCO_{3\ (aq)}$, diluted with dichloromethane and the layers were separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, decanted and concentrated *in vacuo* to give the product. Purification, if needed was performed as indicated.



tert-Butyl 4-chloropyridin-3-yl(phenyl)carbamate (95h)

Following general procedure F, Copper (I) Iodide (83 mg, 0.44 mmol), potassium phosphate (1.86 g, 8.74 mmol) and tert-butyl 4-chloropyridin-3-ylcarbamate (**94**) (1.0 g, 4.37 mmol), **L2** (0.11 mL, 0.87 mmol), and iodobenzene (0.54 mL, 4.81 mmol) were combined in an oven-dried 50 mL Schlenk tube. The reaction was stirred at 110 °C for 18h, cooled to RT, diluted with EtOAc and filtered through a Celite plug. The crude mixture was purified on a silica gel column, eluting with 30% EtOAc / hexanes to give 1.28 g of a light yellow solid. (96%)

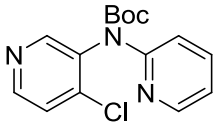
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.50 (s, 1H), 8.39 (d, *J* = 5.4 Hz, 1H), 7.39 (d, *J* = 5.1 Hz, 1H), 7.33 – 7.21 (m, 4H), 7.18 – 7.11 (m, 1H), 1.42 (s, 9H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 152.8, 151.6, 148.9, 143.0, 141.3, 137.3, 128.9, 126.0, 125.6, 125.0, 82.1, 28.1

FT-IR: (NaCl, thin film) ν = 2977, 2932, 1719, 1559, 1319, 1160, 691 cm^{-1}.

EA: Calculated: $C_{16}H_{17}ClN_2O_2$, C; 63.05; H, 5.62; N, 9.19; found C, 63.29; H, 5.45; N, 9.39

MP: 85 – 87 °C



tert-butyl 4-chloropyridin-3-yl(pyridin-2-yl)carbamate (SI5)

Following general procedure F, Copper (I) Iodide (83 mg, 0.44 mmol), potassium phosphate (1.86 g, 8.74 mmol) and tert-butyl 4-chloropyridin-3-ylcarbamate (**94**) (1.0 g, 4.37 mmol), **L2** (0.11 mL, 0.87 mmol), and 2-bromopyridine (0.46 mL, 4.81 mmol) were combined in an oven-dried 50 mL Schlenk tube. The reaction was stirred at 110 °C for 22h, cooled to RT, diluted with EtOAc and filtered through a Celite plug. The crude mixture was purified on a silica gel column, eluting with 20% EtOAc / hexanes to give 1.33 g of a white crystalline solid. (97%)

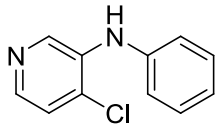
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.50 (s, 1H), 8.44 (d, *J* = 5.1 Hz, 1H), 8.19 (ddd, *J* = 0.9 Hz, 1.8 Hz, 4.8 Hz, 1H), 7.89 (td, *J* = 0.9 Hz, 8.4 Hz, 1H), 7.69 (ddd, *J* = 2.1 Hz, 7.2 Hz, 8.4 Hz, 1H), 7.41 (d, *J* = 5.4 Hz, 1H), 6.99 (ddd, *J* = 0.9 Hz, 4.8 Hz, 7.5 Hz, 1H), 1.41 (s, 9H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 153.7, 152.5, 152.0, 149.0, 147.9, 143.2, 137.6, 136.2, 124.7, 120.0, 118.2, 82.7, 28.0

FT-IR: (NaCl, thin film) ν = 2979, 2934, 1721, 1588, 1467, 1436, 1158, 1111, 845, 781 cm^{-1}.

EA: Calculated: $C_{15}H_{16}ClN_3O_2$, C; 58.92; H, 5.27; N, 13.74; found C, 58.61; H, 5.31; N, 13.86

MP: 92 – 94 °C



4-chloro-N-phenylpyridin-3-amine (94h)

Following general procedure G, tert-Butyl 4-chloropyridin-3-yl(phenyl)carbamate (**95h**) (1.12 g, 3.67 mmol) was combined with dichloromethane (7.3 mL) and TFA (2.45 mL), and stirred 24h. The reaction mixture was poured into sat. $NaHCO_{3\ (aq)}$, diluted with dichloromethane and the layers were separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, decanted and concentrated *in vacuo* to give the product as a tan microcrystalline solid. (732 mg, 97%)

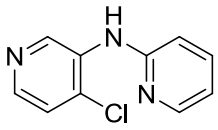
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.56 (s, 1H), 8.02 (d, *J* = 5.1 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.28 (d, *J* = 5.1 Hz, 1H), 7.21 – 7.17 (m, 2H), 7.15 – 6.95 (m, 1H), 5.98 (br s, 1H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 141.2, 140.5, 138.0, 137.6, 130.0, 129.8, 124.4, 123.7, 120.6

FT-IR: (NaCl, thin film) ν = 3106, 3031, 1596, 1560, 1496, 1406, 1328, 1233, 1075, 816, 755, 696 cm^{-1}.

EA: Calculated: $C_{11}H_9ClN_2$, C; 64.56; H, 4.43; N, 13.69; found C, 64.86; H, 4.66; N, 13.86

MP: 107 – 109°C



N-(4-chloropyridin-3-yl)pyridin-2-amine (SI6)

Following general procedure G, tert-butyl 4-chloropyridin-3-yl(pyridin-2-yl)carbamate (**SI5**) (1.0 g, 3.27 mmol) was combined with dichloromethane (6.5 mL) and TFA (2.2 mL), and stirred 8h. The reaction mixture was poured into sat. $NaHCO_{3\ (aq)}$, diluted with dichloromethane and the layers were separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, decanted and concentrated *in vacuo* to give the product as an off-white microcrystalline solid. (645 mg, 96%)

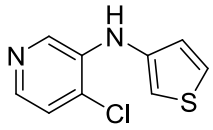
^{1}H NMR (300 MHz, $CDCl_3$) δ= 9.46 (s, 1H), 8.30 – 8.25 (m, 1H), 8.14 (d, *J* = 5.1 Hz, 1H), 7.57 (ddd, *J* = 1.8 Hz, 7.2 Hz, 8.1 Hz, 1H), 7.31 (d, *J* = 5.1 Hz, 1H), 6.89 – 6.83 (m, 2H), 6.75 (br s, 1H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 154.2, 148.3, 143.0, 142.0, 138.1, 134.8, 131.7, 124.2, 116.8, 110.4

FT-IR: (NaCl, thin film) ν = 3057, 1609, 1558, 1520, 1482, 1421, 1334, 1310, 771 cm^{-1}.

EA: Calculated: $C_{10}H_8ClN_3$, C; 58.41; H, 3.92; N, 20.43; found C, 58.57; H, 3.98; N, 20.19

MP: 122 – 123°C



4-chloro-N-(thiophen-3-yl)pyridin-3-amine (SI7)

Following general procedure F, Copper (I) Iodide (83 mg, 0.44 mmol), potassium phosphate (1.86 g, 8.74 mmol) and tert-butyl 4-chloropyridin-3-ylcarbamate (**94**) (1.0 g, 4.37 mmol), **L2** (0.11 mL, 0.87 mmol), and 3-bromothiophene (0.45 mL, 4.81 mmol) were combined in an oven-dried 50 mL Schlenk tube. The reaction was stirred at 110 °C for 22h, cooled to RT, diluted with EtOAc (10 mL) and filtered through a Celite plug to give the crude product which was purified on a silica gel column eluted with 20% EtOAc / Hexanes. 800 mg of the product was isolated as a mixture with tert-butyl 4-chloropyridin-3-ylcarbamate. This mixture was taken on as is to the next step.

Following general procedure G, the crude coupled product was combined with dichloromethane (5.1 mL) and TFA (1.7 mL), and stirred 7h. The reaction was poured into sat. $NaHCO_{3\ (aq)}$, diluted with dichloromethane and the layers were separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, decanted and concentrated *in vacuo.* This mixture was purified on a silica gel column, eluting with 20% EtOAc / hexanes to give the product as a white microcrystalline solid. (495 mg, 54% over two steps)

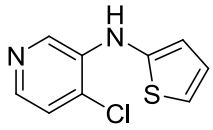
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.41 (s, 1H), 7.97 (d, *J* = 5.1 Hz, 1H), 7.32 (dd, *J* = 3.0 Hz, 5.1 Hz, 1H), 7.24 (d, *J* = 5.1 Hz, 1H), 6.98 (dd, *J* = 1.5 Hz, 5.1 Hz, 1H), 6.95 – 6.90 (m, 1H), 6.06 (br s, 1H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 140.5, 138.6, 138.5, 136.6, 128.4, 126.1, 124.1, 123.7, 111.9

FT-IR: (NaCl, thin film) ν = 3027, 1580, 1523, 1459, 1415, 1324, 1238, 1074, 825, 763 cm^{-1}.

EA: Calculated: $C_9H_7ClN_2S$, C; 51.31; H, 3.35; N, 13.30; found C, 51.35; H, 3.50; N, 13.35

MP: 110 – 111°C



4-chloro-N-(thiophen-2-yl)pyridin-3-amine (SI8)

Following general procedure F, Copper (I) Iodide (83 mg, 0.44 mmol), potassium phosphate (1.86 g, 8.74 mmol) and tert-butyl 4-chloropyridin-3-ylcarbamate (**94**) (1.0 g, 4.37 mmol), **L2** (0.11 mL, 0.87 mmol), and 2-bromothiophene (0.47 mL, 4.81 mmol) were combined in an oven-dried 50 mL Schlenk tube. The reaction was stirred at 110 °C for 24h, cooled to RT, diluted with EtOAc and filtered through a Celite plug to give the crude product which was purified on a silica gel column eluted with 30% EtOAc / hexanes. 1.12 g of the product was isolated as a mixture with tert-butyl 4-chloropyridin-3-ylcarbamate. This mixture was taken on as is to the next step.

Following general procedure G, the crude coupled product was combined with dichloromethane (7.2 mL) and TFA (2.4 mL), and stirred for18h. The reaction was poured into sat. $NaHCO_{3\ (aq)}$, diluted with dichloromethane and the layers were separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, decanted and concentrated *in vacuo.* This mixture was purified on a silica gel column, eluting with 20% EtOAc / hexanes to give the product as a brown microcrystalline solid. (530 mg, 58% over two steps)

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.22 (s, 1H), 7.96 (d, *J* = 5.1 Hz, 1H), 7.20 (d, *J* = 5.1 Hz, 1H), 7.07 (dd, *J* = 1.2 Hz, 5.7 Hz, 1H), 6.92 (dd, *J* = 3.9 Hz, 5.7 Hz), 6.88 – 6.82 (m, 1H), 6.11 (br s, 1H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 142.3, 140.6, 139.6, 136.3, 127.8, 126.2, 123.8, 122.6, 122.1

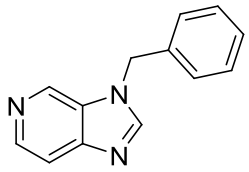
FT-IR: (NaCl, thin film) ν = 1574, 1543, 1496, 1438, 1408, 1320, 1159, 1073, 814, 696 cm^{-1}.

EA: Calculated: $C_9H_7ClN_2S$, C; 51.31; H, 3.35; N, 13.30; found C, 51.36; H, 3.55; N, 13.25

MP: 105 – 107°C

General Procedure H: Cyclization of 3-amino-4-chloropyridines

To an oven-dried 25 mL Schlenk tube equipped with a stirbar was added $Pd_2(dba)_3 \cdot CHCl_3$ (1 mol %), $Me_3(OMe)$*t*-BuXPhos (5 mol %), K_3PO_4 (1.5 eq.) and the pyridine (1 eq.). The reaction vessel was evacuated under vacuum and refilled with $Ar_{(g)}$. *t*-BuOH (0.2 M) & formamide (1.5 eq.) were then added via syringe and the reaction mixture was degassed by three vacuum/$Ar_{(g)}$ purge cycles. The reaction vessel was then equipped with a cold-finger condenser, and placed in a pre-heated 110 °C oil-bath and stirred for the specified time. Upon consumption of the pyridine (as judged by TLC analysis) the reaction was allowed to cool to RT, diluted with methanol, and passed through a Celite plug, washing with additional methanol. The crude product was concentrated *in vacuo*, and applied to a silica gel column, eluting with the specified eluent.

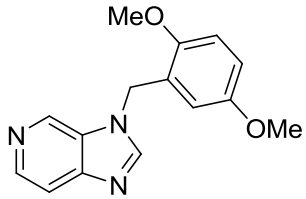


3-benzyl-3H-imidazo[4,5-*c*]pyridine (96a)[214]

4-Chloro-N-benzylpyridin-3-amine (88 mg, 0.4 mmol) was reacted following general procedure H for 4 h. The crude material was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to yield the product as a beige solid (70 mg, 84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.70 (d, *J* = 0.9 Hz, 1H), 8.43 (d, *J* = 5.4 Hz, 1H), 8.04 (s, 1H), 7.70 (dd, *J* = 0.9 Hz, 5.4 Hz, 1H), 7.39 – 7.28 (m, 3H), 7.25 – 7.17 (m, 2H), 5.40 (s, 2H)

MP: 134 - 135 °C



3-(2,5-dimethoxybenzyl)-3H-imidazo[4,5-*c*]pyridine (96b)

4-chloro-N-(2,5-dimethoxybenzyl)pyridin-3-amine (112 mg, 0.4 mmol) was reacted following general procedure H for 6.5 h. The crude product was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to yield the product as a beige solid (92 mg, 85%).

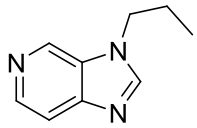
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.83 (d, *J* = 0.6 Hz, 1H), 8.38 (d, *J* = 5.4 Hz, 1H), 8.06 (s, 1H), 7.65 (dd, *J* = 5.7 Hz, 0.9 Hz, 1H), 6.79 (app d, *J* = 1.5 Hz, 2H), 6.73 (app t, *J* = 1.5 Hz, 1H), 5.32 (s, 2H), 3.75 (s, 3H), 3.68 (s, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 153.6, 151.5, 138.8, 146.3, 141.8, 133.9, 131.8, 123.7, 116.2, 115.0, 114.1, 111.7, 55.8, 55.8, 45.0

FT-IR (NaCl, thin film) ν = 2968, 2936, 2878, 1650, 1610, 1492, 1461, 1383, 1309, 1264, 1211, 907, 826 cm^{-1}.

EA: Calculated: $C_{15}H_{15}N_3O_2$, C; 66.90; H, 5.61; N, 15.60; found C, 66.79; H, 5.24; N, 15.59

MP: 125 °C (decomposition)



3-Propyl-3H-imidazo[4,5-*c*]pyridine (96g)

4-Chloro-N-propylpyridin-3-amine (68 mg, 0.4 mmol) was reacted following general procedure H for 6.5 h. The crude product was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to yield the product as a beige solid (55 mg, 85%).

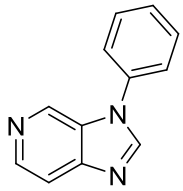
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.85 (s, 1H), 8.43 (d, *J* = 5.7 Hz, 1H), 7.98 (s, 1H), 7.69 (dd, *J* = 5.4 Hz, 0.9 Hz, 1H), 4.21 (t, *J* = 6.9 Hz, 2H), 1.95 (sext, *J* = 7.2 Hz, 2H), 0.95 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 149.0, 145.8, 141.9, 133.5, 131.7, 115.2, 47.4, 23.4, 11.4

FT-IR (NaCl, thin film) ν = 2969, 2880, 1655, 1609, 1492, 1460, 1383, 1309, 1264, 1211, 1166, 1126, 1027, 906, 825 cm^{-1}.

EA: Calculated: $C_9H_{11}N_3$, C; 67.06; H, 6.88; N, 26.07; found C, 67.10; H, 6.99; N, 26.06

MP: 75 - 78 °C



3-phenyl-3H-imidazo[4,5-*c*]pyridine (96h)

4-Chloro-N-phenylpyridin-3-amine (82 mg, 0.4 mmol) was reacted following general procedure H for 6.5 h. The crude product was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to yield the product as a beige solid (70 mg, 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.91 (s, 1H), 8.46 (d, *J* = 5.7 Hz, 1H), 8.19 (s, 1H), 7.72 (dd, *J* = 0.6 Hz, 5.4 Hz, 1H), 7.61 – 7.41 (m, 5H)

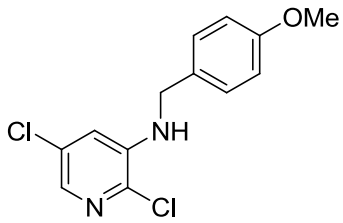
^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 149.1, 144.8, 142.5, 135.4, 134.2, 131.4, 130.3, 128.7, 123.8, 115.2

FT-IR (NaCl, thin film) ν = 3177, 1597, 1503, 1480, 1304, 1233, 761, 696 cm^{-1}.

EA: Calculated: $C_{12}H_9N_3$, C; 73.83; H, 4.65; N, 21.52; found C, 73.80; H, 4.90; N, 21.28

MP: 149 – 150 °C

7.7 REGIOSELECTIVE AMIDATION OF POLYCHLORINATED AMINOPYRIDINES



2,5-Dichloro-N-(4-methoxybenzyl)pyridin-3-amine (101)

To a flame-dried 50 mL RBF was added 3-amino-2,5-dichloropyridine (1.0 g, 6.13 mmol), 10 mL ethyl acetate, *p*-methoxybenzaldehyde (0.82 mL, 6.75 mmol). The mixture was allowed to stir until complete dissolution at which time trifluoroacetic acid (0.94 mL, 12.3 mmol) was added as a single portion. After stirring for 2 min sodium triacetoxyborohydride (1.56 g, 7.4 mmol) was added portionwise. The reaction was stirred for 30 minutes at which time the chloropyridine was consumed by TLC; the reaction was quenched with 20% NaOH and the pH was adjusted to ~8 with $NaOH_{(s)}$. The layers were separated, the organic layer washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 1.87 g crude material which was recrystalized from 60 mL 2:1 Hexanes:Ethyl acetate to give **101** as a purple crystalline solid (1.68 g, 97%)

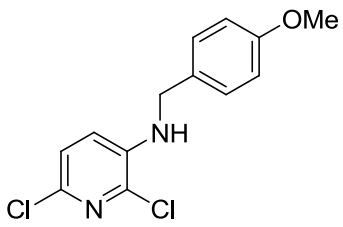
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.67 (d, *J* = 2.1 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 2.4 Hz, 1H). 4.79 (br s, 1H), 4.29 (d, *J* = 5.1 Hz, 2H), 3.82 (s, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 159.7, 141.4, 135.3, 134.9, 132.0, 129.2, 129.0, 117.6, 114.8, 55.7, 47.3

FT-IR: (NaCl, thin film) ν = 3308, 1610, 1577, 1512, 1499, 1358, 1252, 1120, 1035 cm^{-1}.

HRMS (ESI) Calc ($C_{13}H_{12}Cl_2N_2O$): 283.0327, Found: 282.0327

MP: 115 – 117 °C



2,6-Dichloro-N-(4-methoxybenzyl)pyridin-3-amine (102)

To a flame-dried 100 mL RBF was added 3-amino,2,6-dichloropyridine (2.5 g, 15.6 mmol), 24 mL of ethyl acetate, *p*-methoxybenzaldehyde (2.08 mL, 17.1 mmol). The mixture was allowed to stir until complete dissolution at which time trifluoroacetic acid (2.31 mL, 31.1 mmol) was added as a single portion. After stirring for 2 min sodium triacetoxyborohydride (3.96 g, 18.7 mmol) was added portionwise. The reaction was stirred for 30 minutes at which time the chloropyridine was consumed by TLC; the reaction was quenched with 20% NaOH and the pH was adjusted to ~8 with $NaOH_{(s)}$. The layers were separated, the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 1.87 g crude material which was recrystalized from 20 mL 2:1 hexanes:EtOAc to give **102** as a white crystalline solid (2.93 g, 66%)

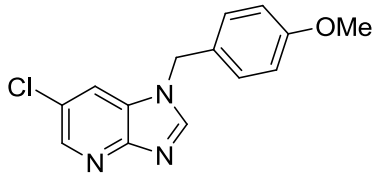
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.25 (d, *J*= 8.4 Hz, 2H), 7.05 (d, *J*= 8.4 Hz, 1H), 6.89 (d, *J*= 8.4 Hz, 2H), 6.84 (d, *J*= 8.4 Hz, 1H), 4.31 (s, 2H), 3.81 (s, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ =159.4, 139.9, 135.9, 134.9, 129.3, 128.5, 123.6, 120.7, 114.5, 55.5, 47.3

FT-IR: (NaCl, thin film) ν = 3366, 1584, 1487, 1095 cm^{-1}.

EA: Calc: C; 55.14, H: 4.27, N: 9.89. Found: C: 55.44, H: 4.34, N: 9.63

MP: 60-63 °C



6-chloro-1-(4-methoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (103)

To an oven-dried 25 mL Schlenk tube equipped with a stirbar was added $Pd_2(dba)_3 \cdot CHCl_3$ (4.1 mg, 0.004 mmol), XantPhos (11.6 mg, 0.02 mmol) K_3PO_4 (128 mg, 0.6 mmol) and the 2,5-Dichloro-N-(4-methoxybenzyl)pyridin-3-amine (**101**) (113 mg, 0.4 mmol). The reaction vessel was evacuated under vacuum and refilled with $Ar_{(g)}$. 1,4-Dioxane and *t*-AmOH (10:1, 0.2 M) were then added via syringe and the reaction mixture was degassed by three vacuum/$Ar_{(g)}$ purge cycles. The reaction vessel was then equipped with a cold-finger, and placed in a pre-heated 110 °C oil-bath and stirred for 6.5 h. The reaction mixture was allowed to cool to RT, diluted with methanol, and passed through a Celite plug, washing with additional methanol. The crude material was concentrated *in vacuo*, and was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to yield the product as a beige solid (105 mg, 96%).

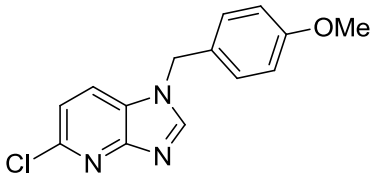
^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.43 (d, *J* = 2.4 Hz, 1H), 8.11 (s, 1H), 7.52 (d, *J* = 2.4 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.24 (s, 2H), 3.76 (s, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 159.9, 154.9, 146.1, 144.0, 128.8, 126.4, 126.2, 126.0, 118.2, 114.7, 55.4, 49.3

FT-IR (NaCl, thin film) ν = 3041, 3003, 2934, 2837, 1611, 1514, 1491, 1406, 1250, 1177, 1032, 917 cm^{-1}.

EA: Calculated: $C_{14}H_{12}ClN_3O$, C; 61.43; H, 4.42; N, 15.35; found C, 61.60; H, 4.72; N, 14.95

MP: 108 – 109 °C



5-chloro-1-(4-methoxybenzyl)-1H-imidazo[4,5-*b*]pyridine (104)

To an oven-dried 25 mL Schlenk tube equipped with a stirbar was added $Pd_2(dba)_3 \cdot CHCl_3$ (4.1 mg, 0.004 mmol), XantPhos (11.6 mg, 0.02 mmol) K_3PO_4 (128 mg, 0.6 mmol) and the 2,6-dichloro-N-(4-methoxybenzyl)pyridin-3-amine (**102**) (113mg, 0.4 mmol). The reaction vessel was evacuated under vacuum and refilled with $Ar_{(g)}$. 1,4-Dioxane and *t*-AmOH (10:1, 0.2 M) were then added via syringe and the reaction mixture was degassed by three vacuum/$Ar_{(g)}$ purge cycles. The reaction vessel was then equipped with a cold-finger condenser, and placed in a pre-heated 110 °C oil-bath and stirred for the 6.5 h. The reaction mixture was allowed to cool to RT, diluted with methanol, and passed through a Celite plug, washing with additional methanol. The crude product was concentrated *in vacuo*, and was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to yield the product as a brown solid (78 mg, 72%).

^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.12 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.15 – 7.10 (m, 3H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.29 (s, 2H), 3.78 (s, 3H)

^{13}C NMR (75.4 MHz, $CDCl_3$) δ= 160.0, 156.0, 146.0, 146.0, 128.9, 126.2, 125.1, 121.0, 118.6, 114.7, 55.4, 49.6

FT-IR (NaCl, thin film) ν = 2935, 2837, 1611, 1514, 1485, 1406, 1352, 1250, 1114, 1031, 920, 807 cm^{-1}.

EA: Calculated: $C_{14}H_{12}ClN_3O$, C; 61.43; H, 4.42; N, 15.35; found C, 61.39; H, 4.43; N, 15.02

MP: 98 – 100 °C

8.0 APPENDEX II: BIBLIOGRAPHY

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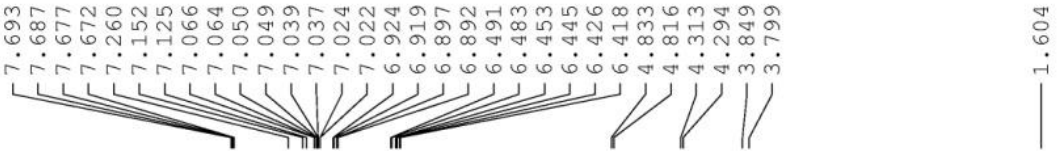
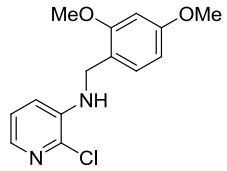
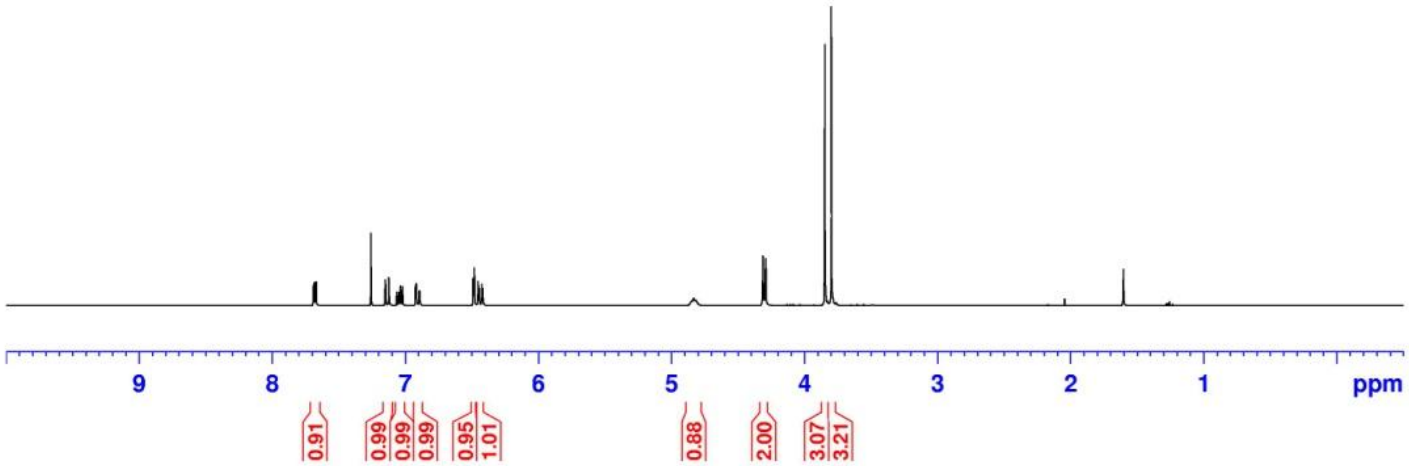
9.0 APPENDEX III: SPECTRA

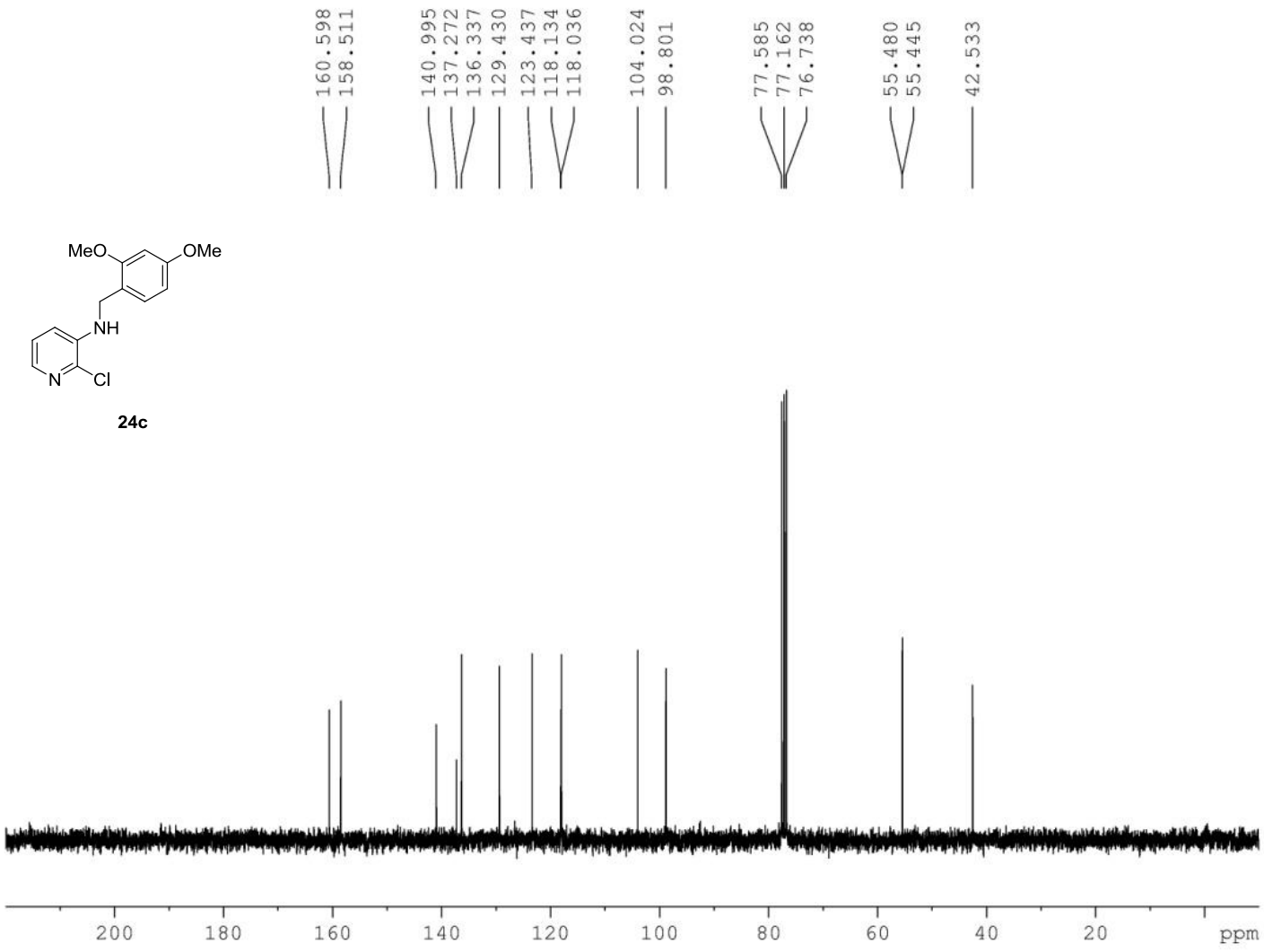
9.1 FIRST GENERATION IMPS


7.693
7.687
7.677
7.672
7.260
7.152
7.125
7.066
7.064
7.050
7.049
7.039
7.037
7.024
7.022
6.924
6.919
6.897
6.892
6.491
6.483
6.453
6.445
6.426
6.418
4.833
4.816
4.313
4.294
3.849
3.799
1.604


MeO
OMe
NH
N
Cl

24c


9
8
7
6
5
4
3
2
1
ppm
0.91
0.99
0.99
0.99
0.95
1.01
0.88
2.00
3.07
3.21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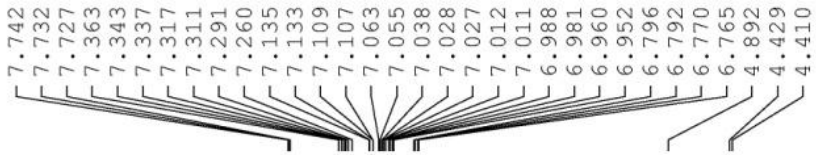
158.511
140.995
137.272
136.337
129.430
123.437
118.134
118.036
104.024
98.801
77.585
77.162
76.738
55.480
55.445
42.533
MeO
OMe
NH
N
Cl
200
180
160
140
120
100
80
60
40
20
ppm

24c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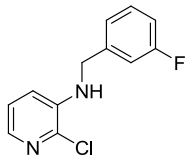
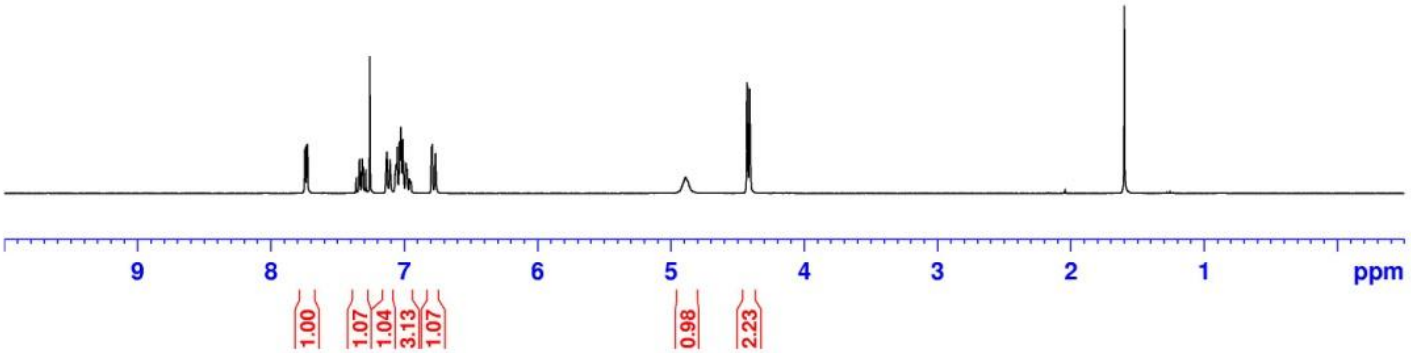
7.732
7.727
7.363
7.343
7.337
7.317
7.311
7.291
7.260
7.135
7.133
7.109
7.107
7.063
7.055
7.038
7.028
7.027
7.012
7.011
6.988
6.981
6.960
6.952
6.796
6.792
6.770
6.765
4.892
4.429
4.410
1.600


F
NH
N
Cl

24d


9
8
7
6
5
4
3
2
1
ppm
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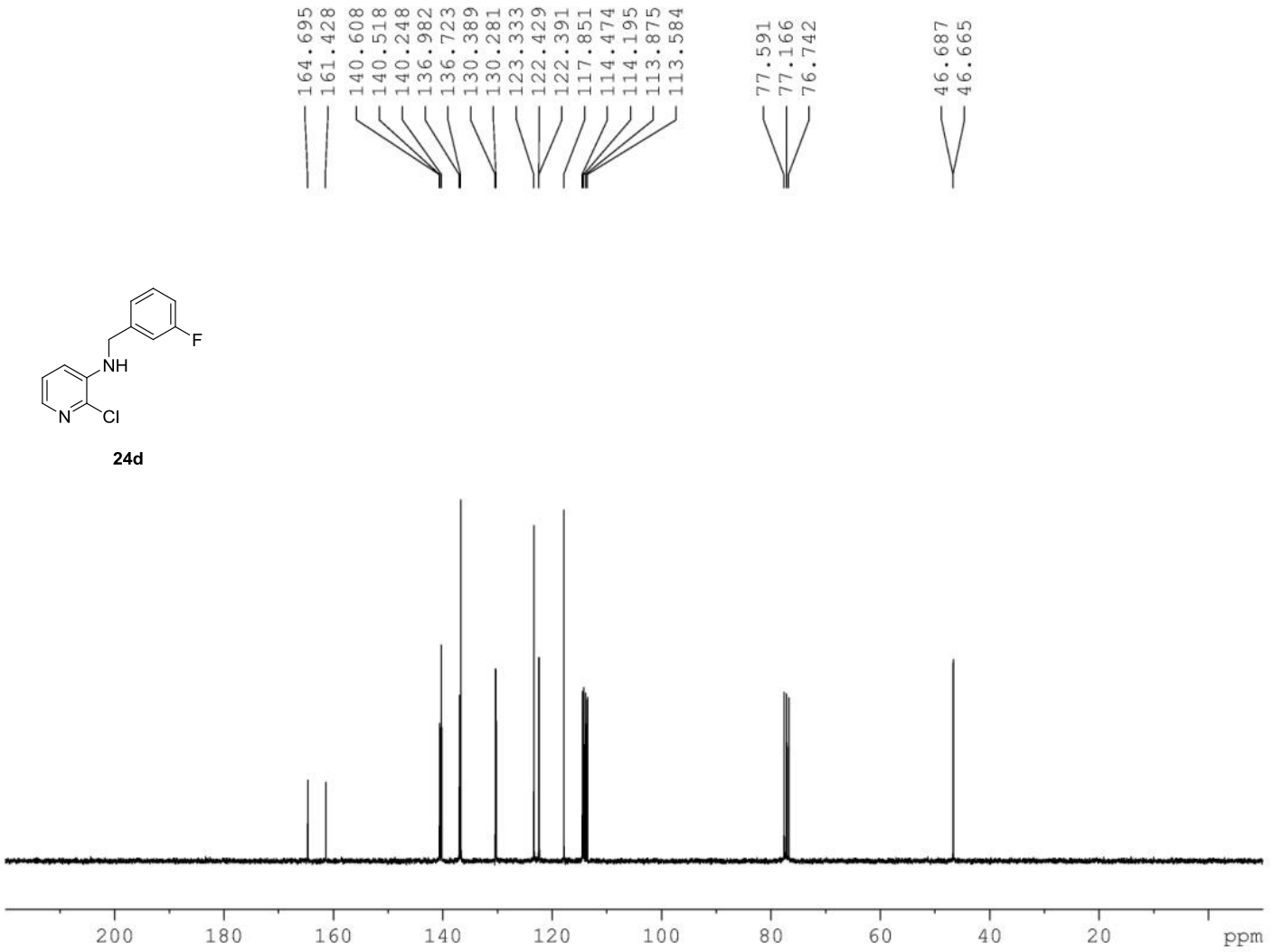
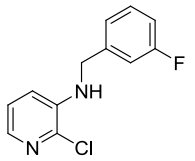
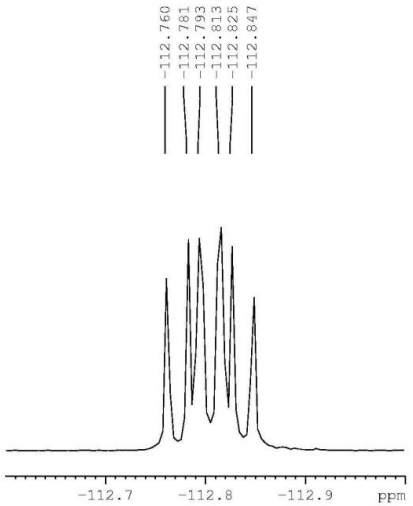
1.07
1.04
3.13
1.07
0.98
2.23


164.695
161.428
140.608
140.518
140.248
136.982
136.723
130.389
130.281
123.333
122.429
122.391
117.851
114.474
114.195
113.875
113.584
77.591
77.166
76.742
46.687
46.665
F
NH
N
Cl
24d
200
180
160
140
120
100
80
60
40
20
ppm


F
NH
N
Cl

24d 19F NMR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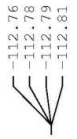
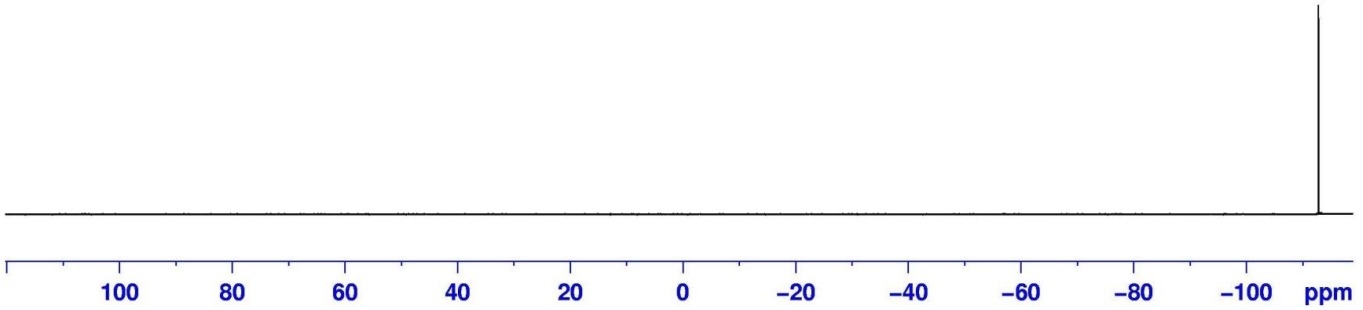
-112.781
-112.793
-112.813
-112.825
-112.847
-112.7
-112.8
-112.9
ppm


-112.76
-112.78
-112.79
-112.81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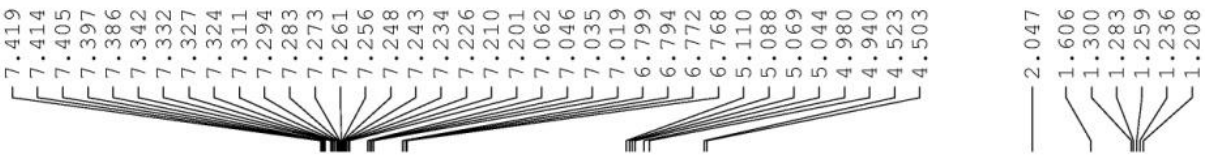
80
60
40
20
0
-20
-40
-60
-80
-100
ppm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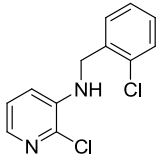
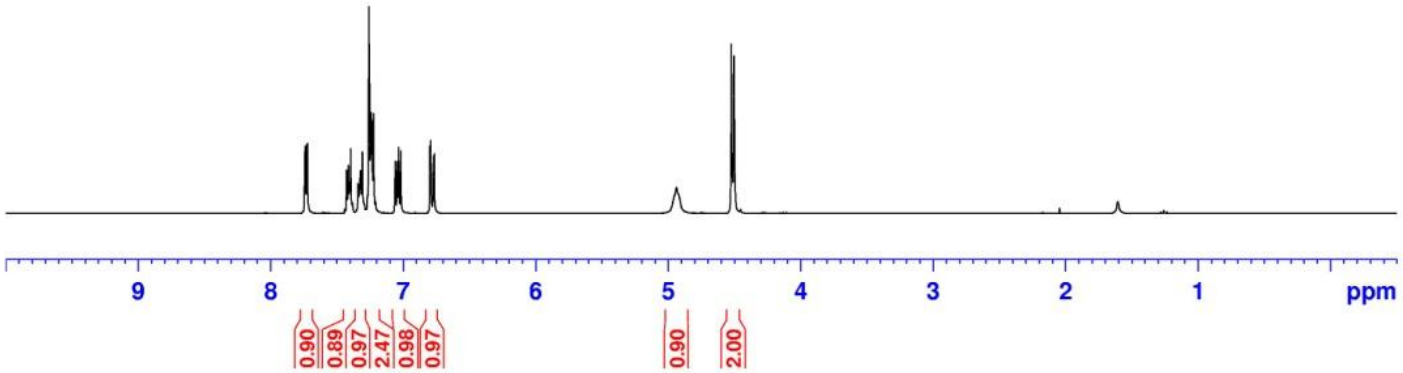
7.414
7.405
7.397
7.386
7.342
7.332
7.327
7.324
7.311
7.294
7.283
7.273
7.261
7.256
7.248
7.243
7.234
7.226
7.210
7.201
7.062
7.046
7.035
7.019
6.799
6.794
6.772
6.768
5.110
5.088
5.069
5.044
4.980
4.940
4.523
4.503
2.047
1.606
1.300
1.283
1.259
1.236
1.208


NH
Cl
N
Cl

24e


9
8
7
6
5
4
3
2
1
ppm
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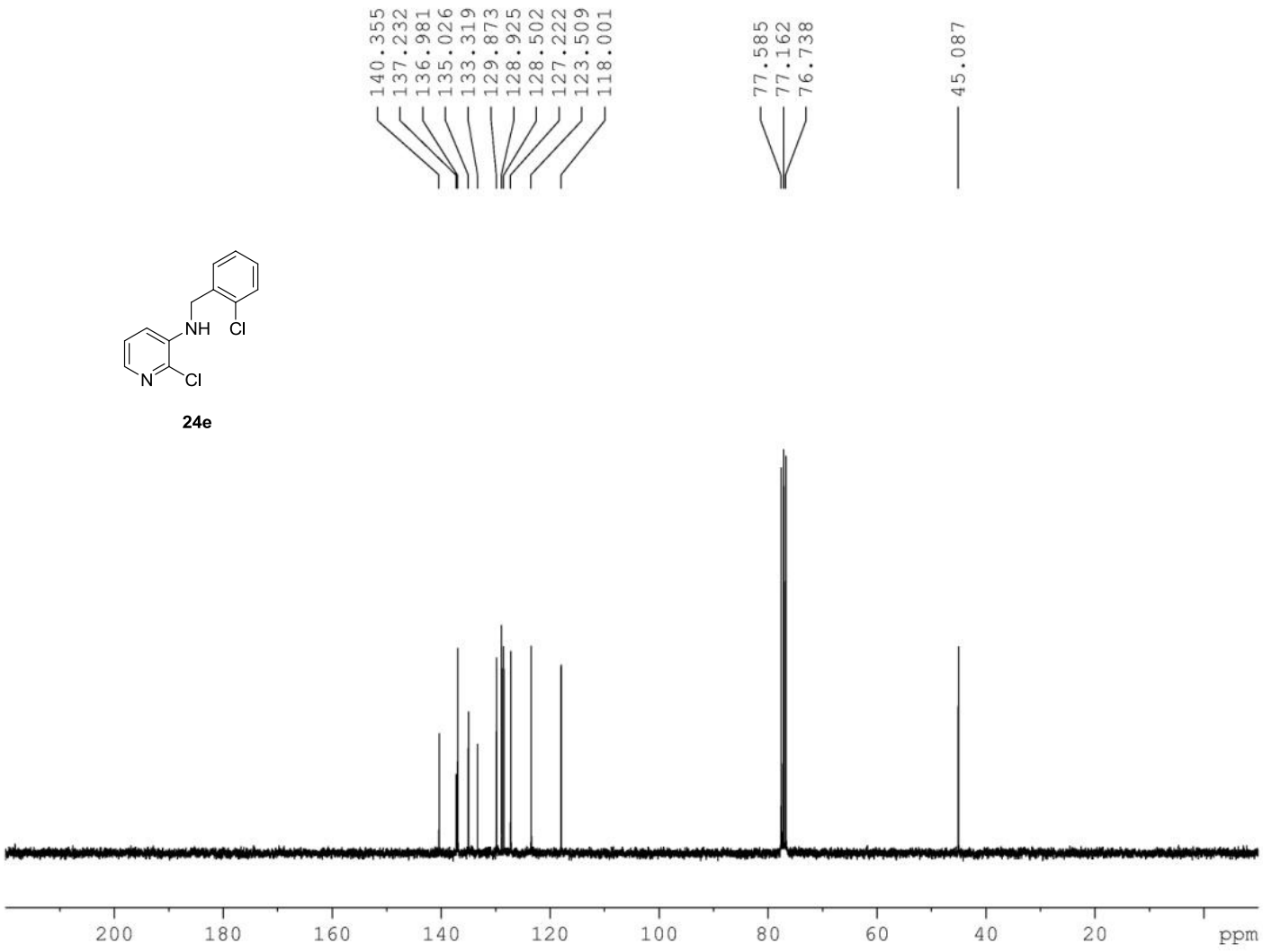
0.89
0.97
2.47
0.98
0.97
0.90
2.00


140.355
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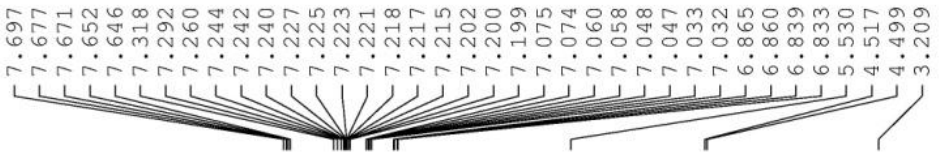
136.981
135.026
133.319
129.873
128.925
128.502
127.222
123.509
118.001
77.585
77.162
76.738
45.087
NH
Cl
N
Cl
200
180
160
140
120
100
80
60
40
20
ppm

24e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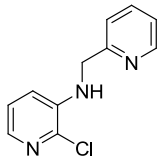
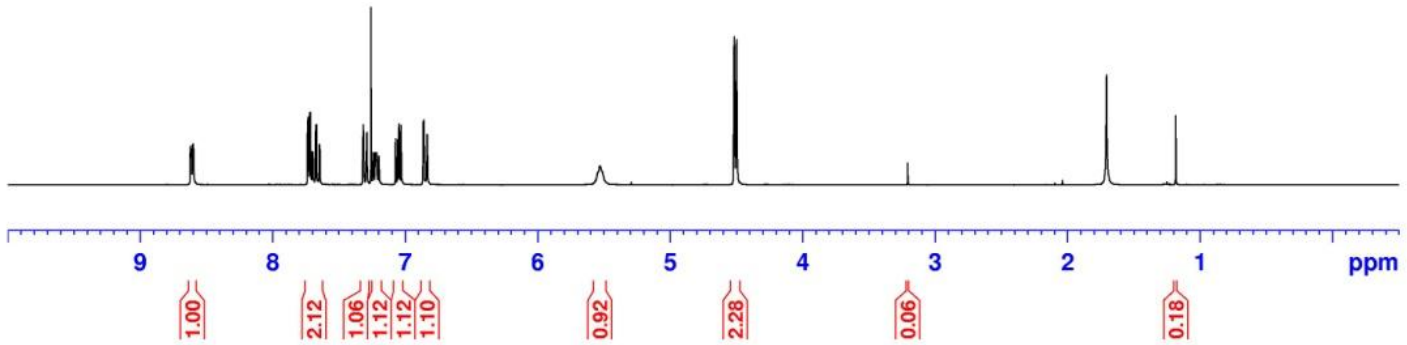
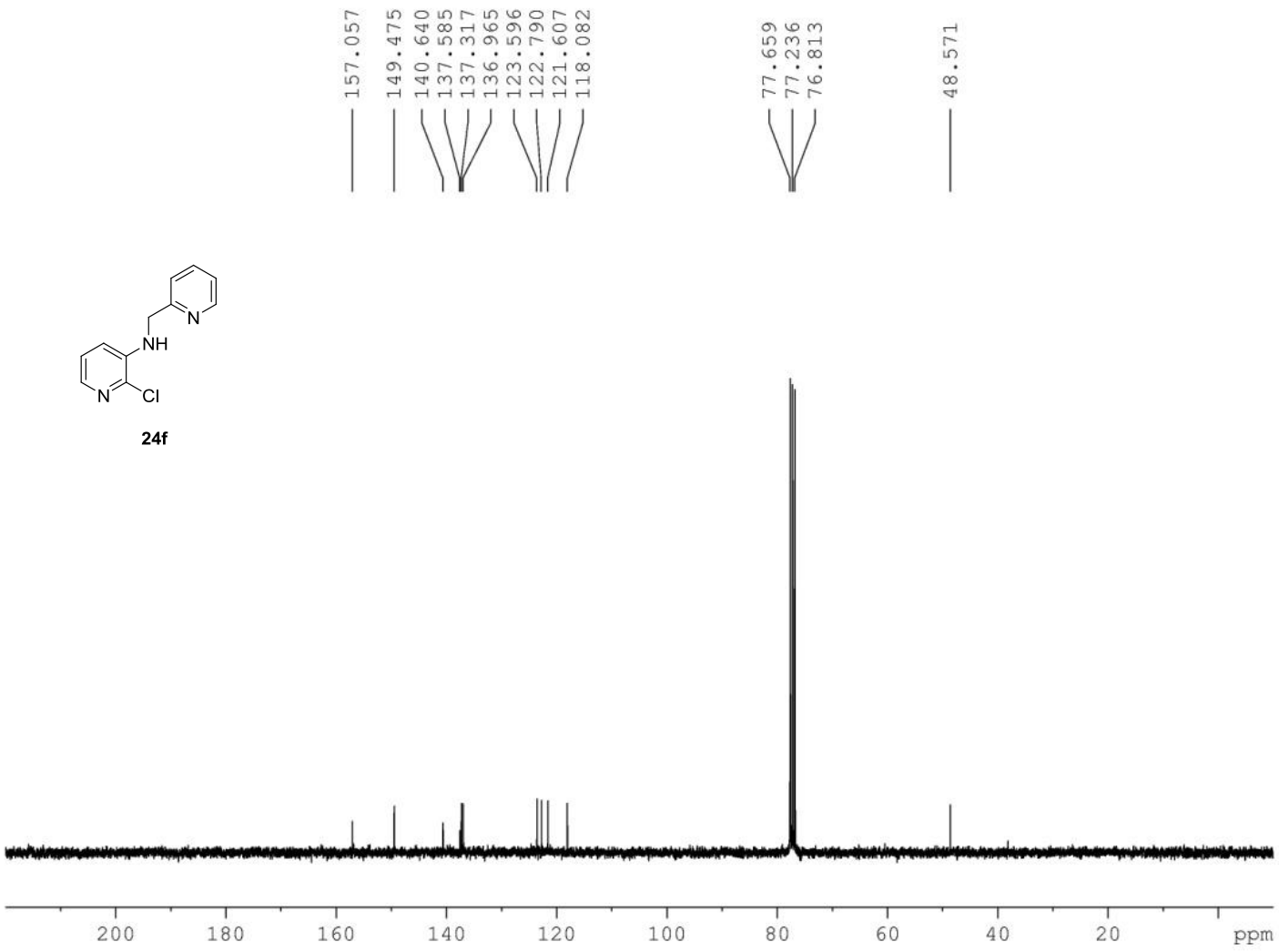
7.677
7.671
7.652
7.646
7.318
7.292
7.260
7.244
7.242
7.240
7.227
7.225
7.223
7.221
7.218
7.217
7.215
7.202
7.200
7.199
7.075
7.074
7.060
7.058
7.048
7.047
7.033
7.032
6.865
6.860
6.839
6.833
5.530
4.517
4.499
3.209
1.707
1.184

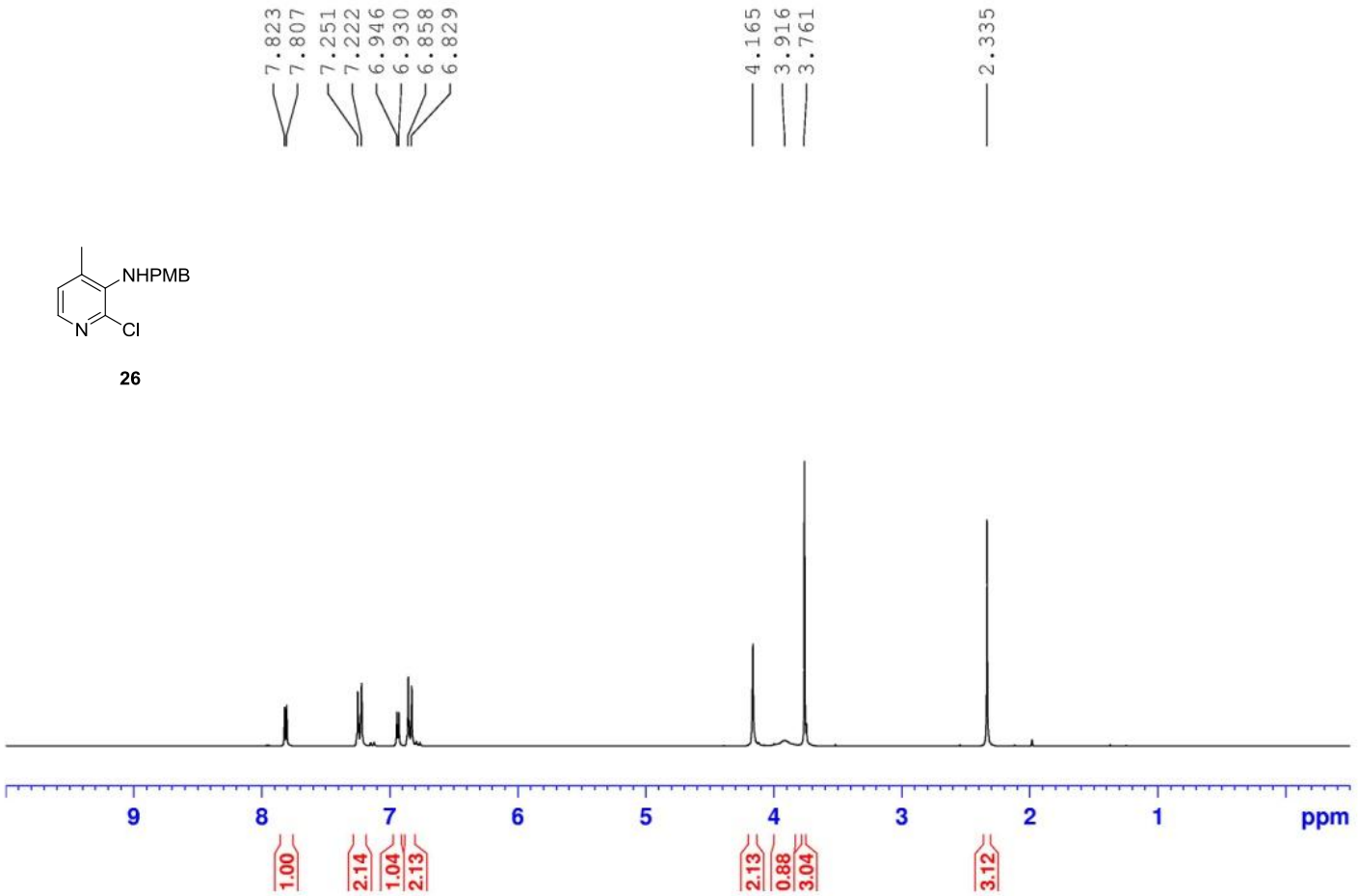

N
NH
N
Cl

24f

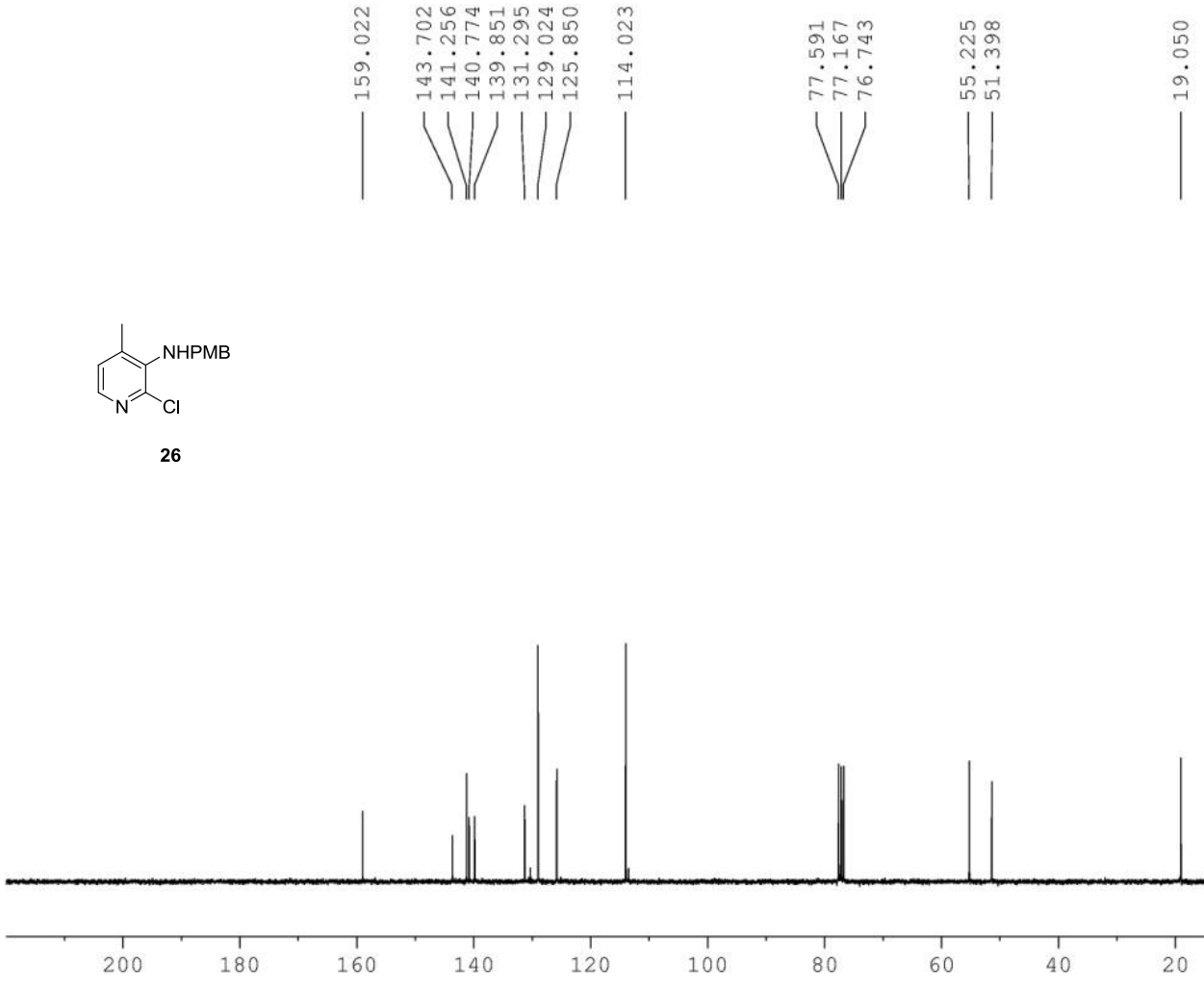

9
8
7
6
5
4
3
2
1
ppm
1.00
2.12
1.06
1.12
1.12
1.10
0.92
2.28
0.06
0.18


157.057
149.475
140.640
137.585
137.317
136.965
123.596
122.790
121.607
118.082
77.659
77.236
76.813
48.571
NH
N
N
Cl
24f
200
180
160
140
120
100
80
60
40
20
ppm

AJR-4-110
Post Column



26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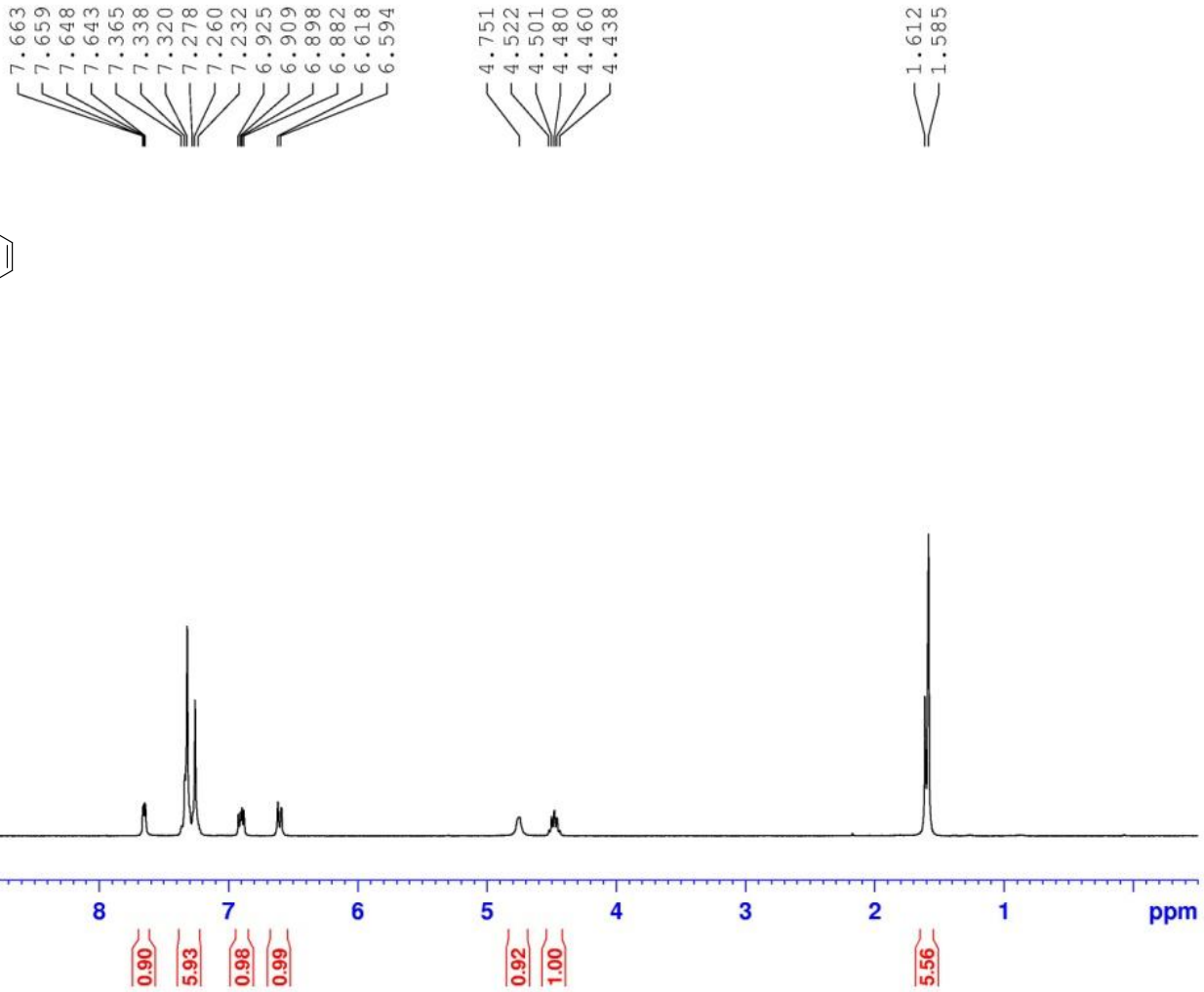
143.702
141.256
140.774
139.851
131.295
129.024
125.850
114.023
77.591
77.167
76.743
55.225
51.398
19.050
NHPMB
N
Cl
200
180
160
140
120
100
80
60
40
20
ppm

26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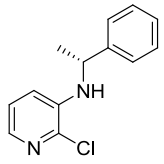
7.648
7.643
7.365
7.338
7.320
7.278
7.260
7.232
6.925
6.909
6.898
6.882
6.618
6.594
4.751
4.522
4.501
4.480
4.460
4.438
1.612
1.585
NH
N
Cl
24m
9
8
7
6
5
4
3
2
1
ppm
0.90
5.93
0.98
0.99
0.92
1.00
5.56

143.578
139.816
137.000
136.542
128.989
127.441
125.689
123.313
118.903

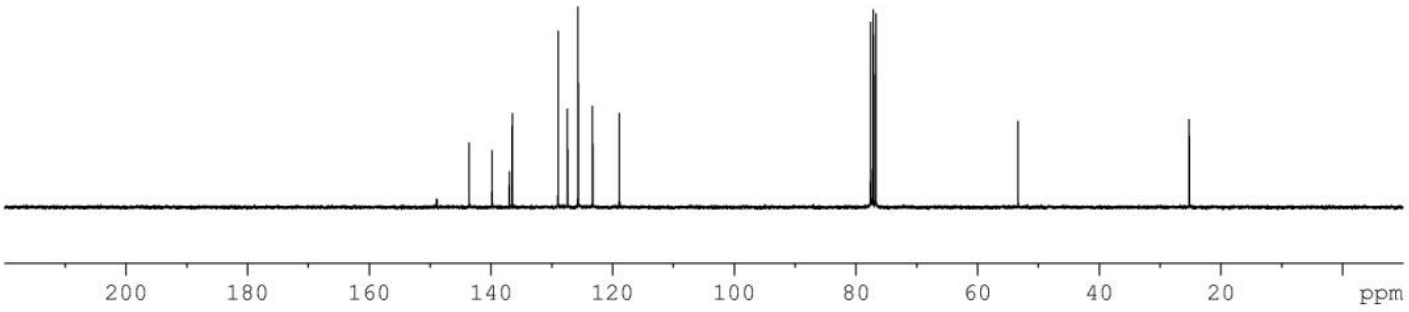
77.586
77.163
76.739

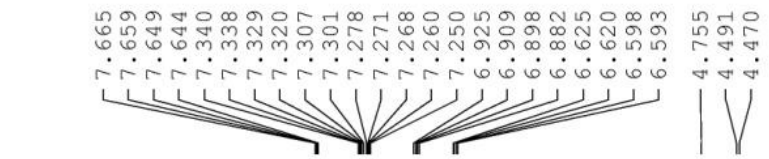
53.328

25.204



24m

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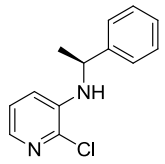
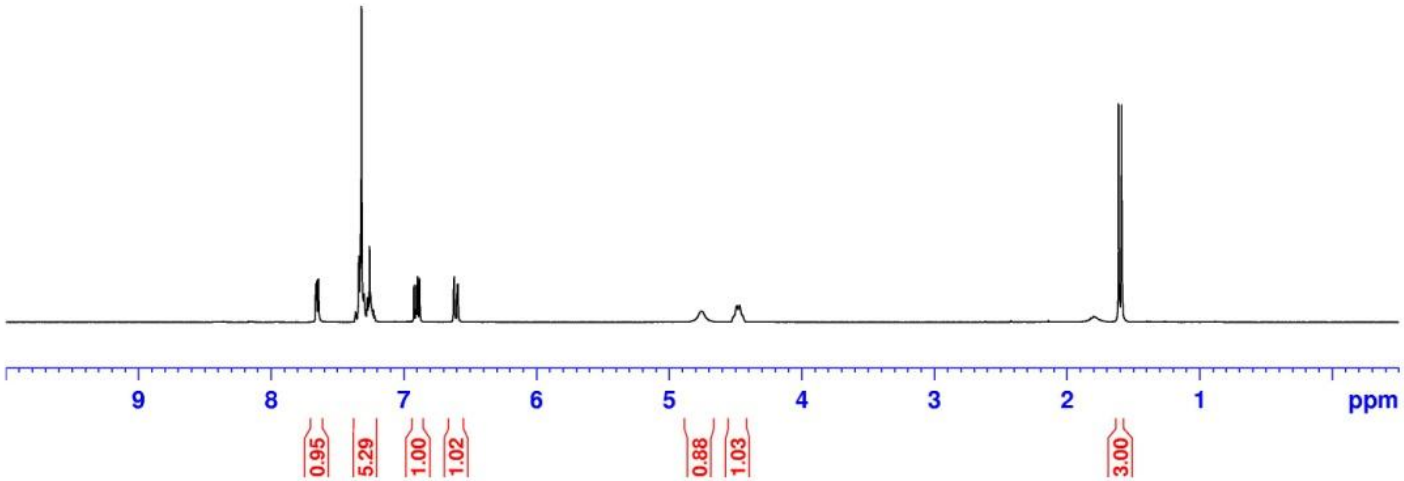
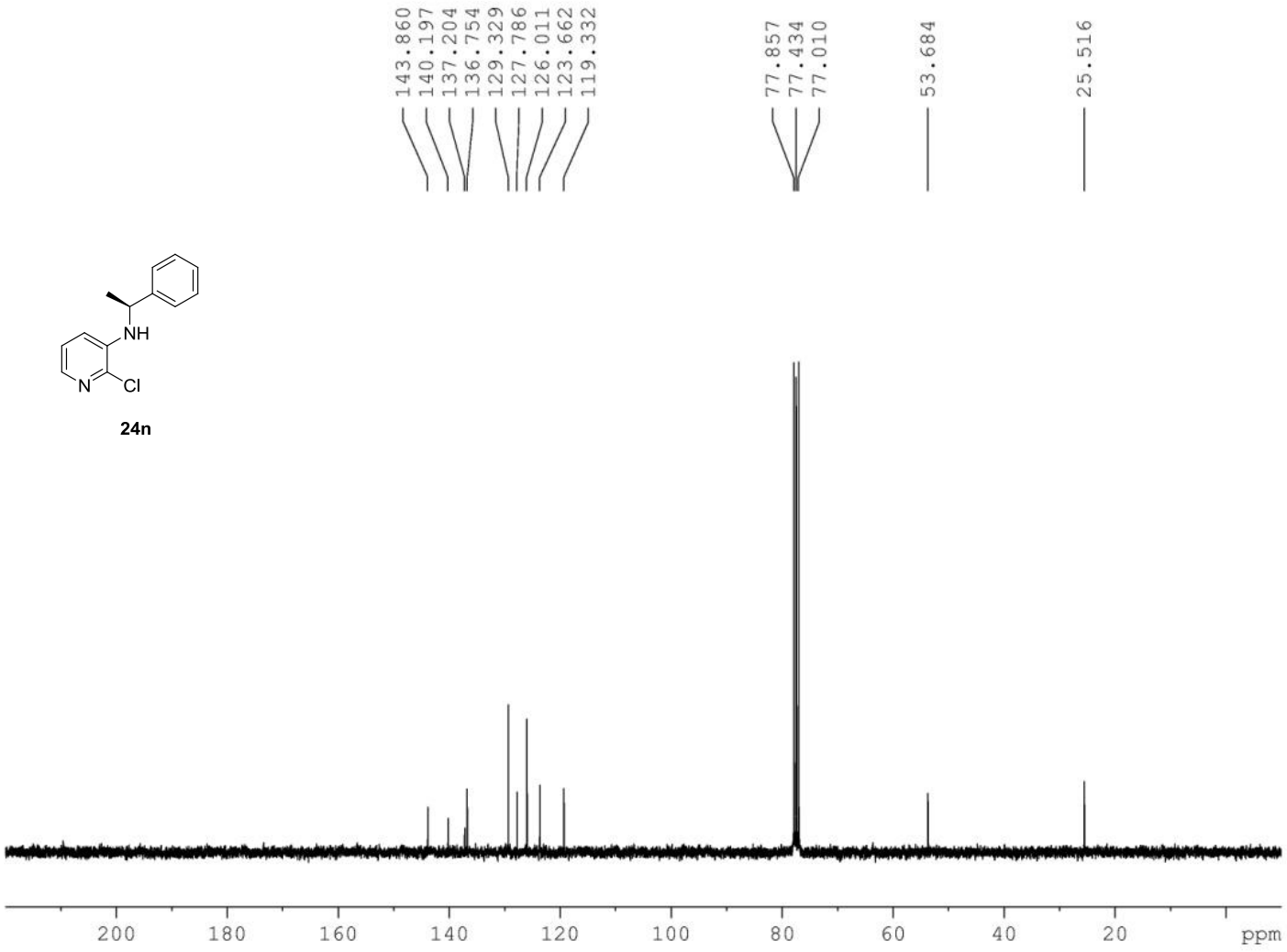
7.340
7.338
7.329
7.320
7.307
7.301
7.278
7.271
7.268
7.260
7.250
6.925
6.909
6.898
6.882
6.625
6.620
6.598
6.593
4.755
4.491
4.470
1.612
1.589

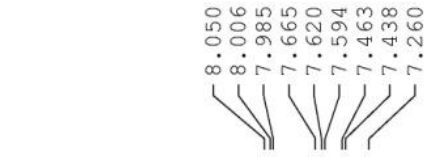

NH
N
Cl

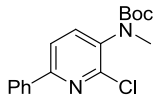
24n


9
8
7
6
5
4
3
2
1
ppm
0.95
5.29
1.00
1.02
0.88
1.03
3.00

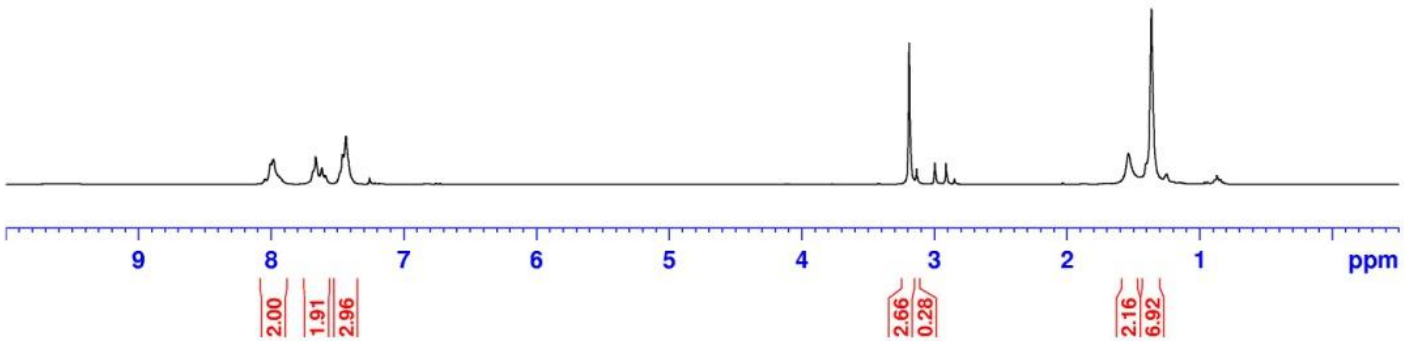

143.860
140.197
137.204
136.754
129.329
127.786
126.011
123.662
119.332
77.857
77.434
77.010
53.684
25.516
NH
N
Cl
200
180
160
140
120
100
80
60
40
20
ppm

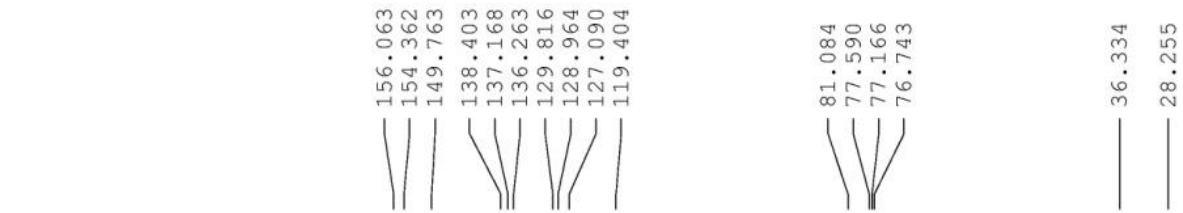
24n


8.050
8.006
7.985
7.665
7.620
7.594
7.463
7.438
7.260
3.192
3.135
2.997
2.913
1.537
1.365


Boc
N
Ph
N
Cl

SI2


9
8
7
6
5
4
3
2
1
ppm
2.00
1.91
2.96
2.66
0.28
2.16
6.92


156.063
154.362
149.763
138.403
137.168
136.263
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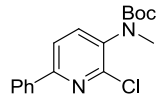
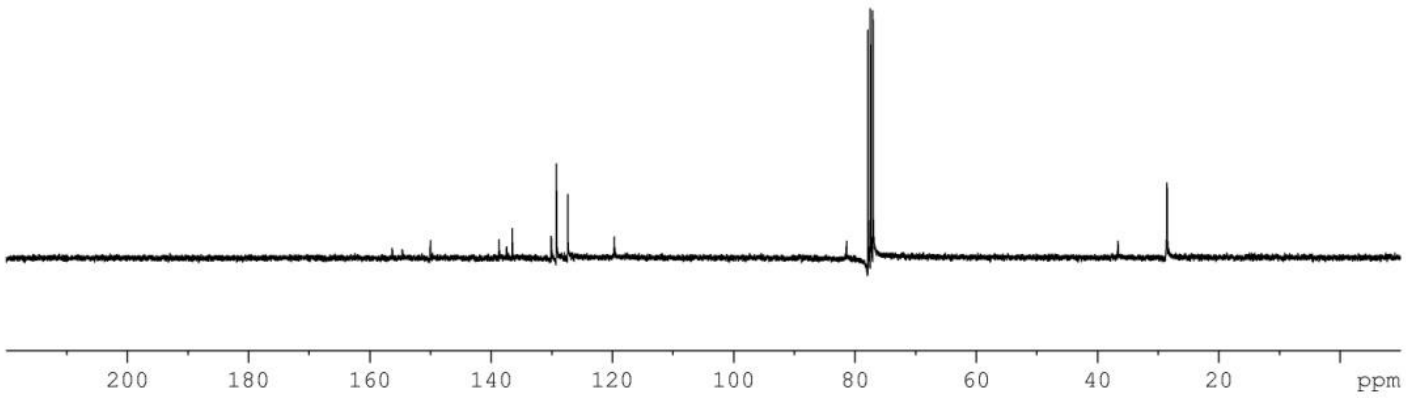
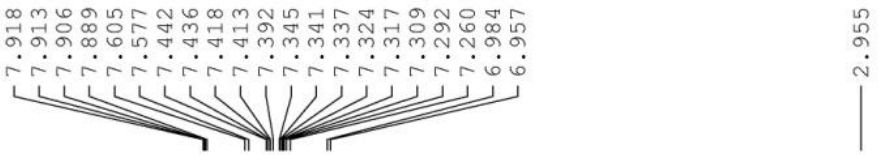
128.964
127.090
119.404
81.084
77.590
77.166
76.743
36.334
28.255

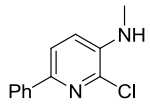

Boc
N
Ph
N
Cl

SI2

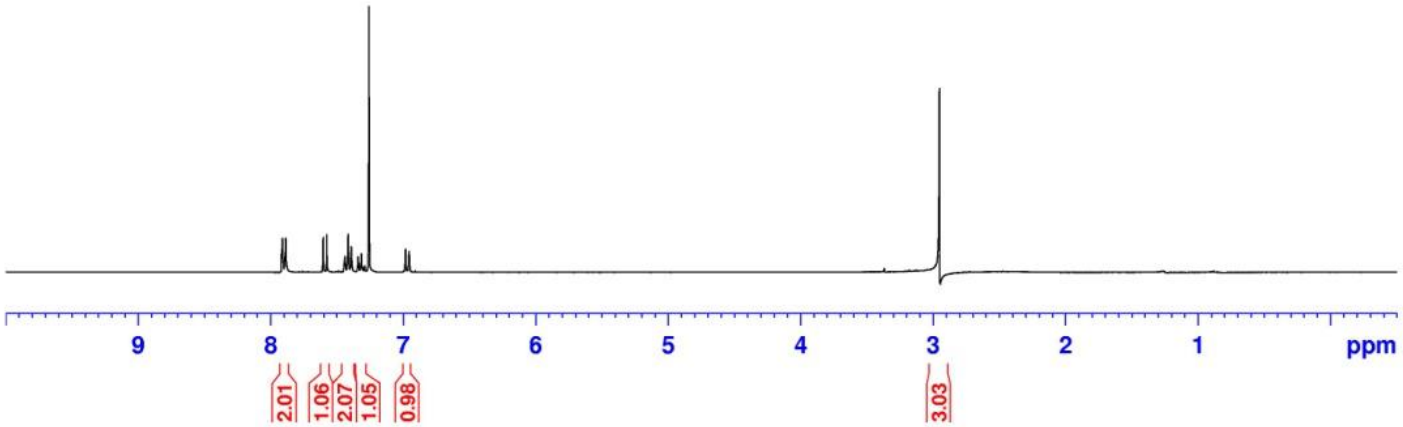

200
180
160
140
120
100
80
60
40
20
ppm

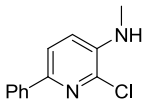
AJR-4-119
Post Column





27

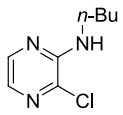



NH
Ph
N
Cl

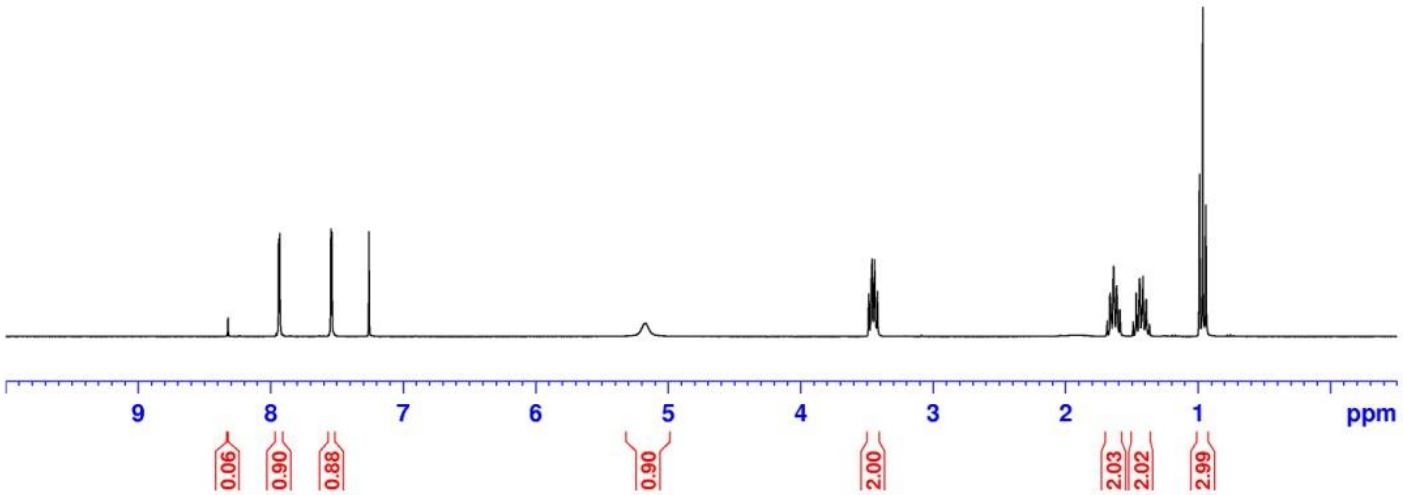
27

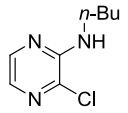
144.764
140.592
138.337
136.731
128.722
127.857
125.845
120.069
117.679
77.587
77.163
76.740
30.148
200
180
160
140
120
100
80
60
40
20
ppm


8.325
7.942
7.933
7.548
7.539
7.260
5.175
3.486
3.468
3.463
3.444
3.439
3.420
1.688
1.665
1.656
1.639
1.631
1.617
1.615
1.590
1.492
1.467
1.441
1.416
1.392
1.368
0.990
0.966
0.941


n-Bu
NH
N
N
Cl

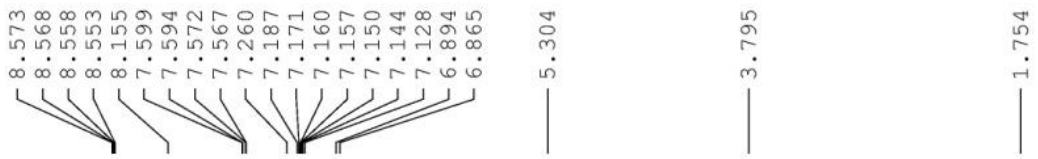
28

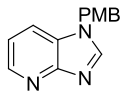

9
8
7
6
5
4
3
2
1
ppm
0.06
0.90
0.88
0.90
2.00
2.03
2.02
2.99


n-Bu
NH
N
N
Cl

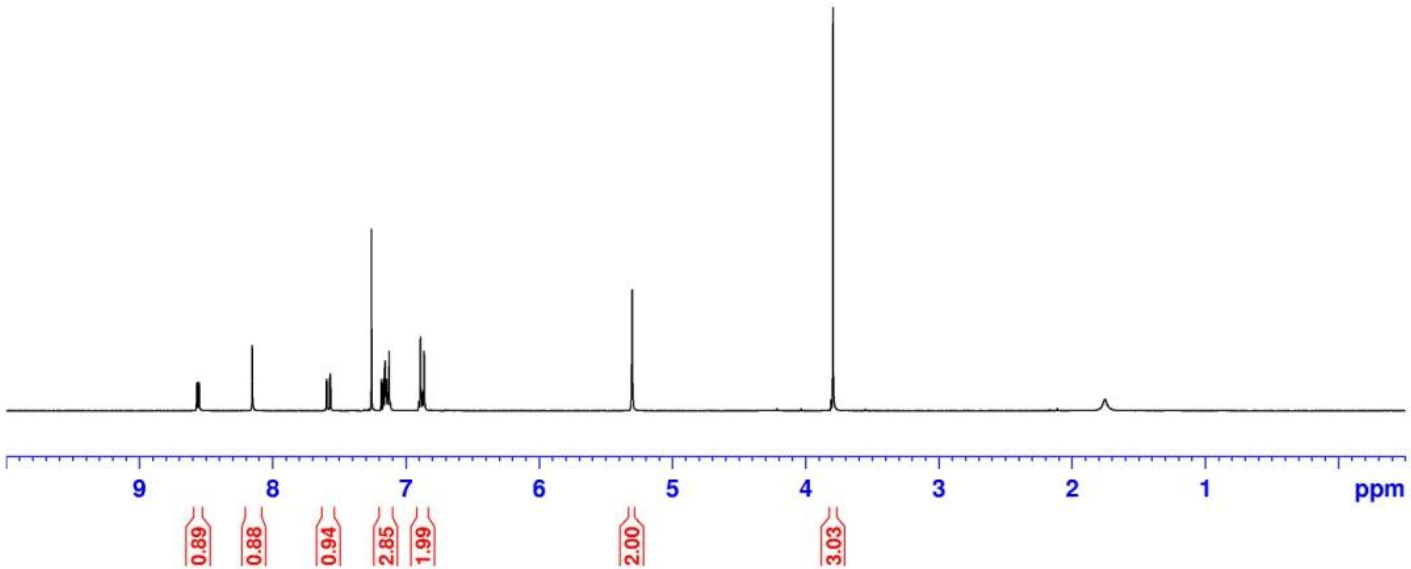
28

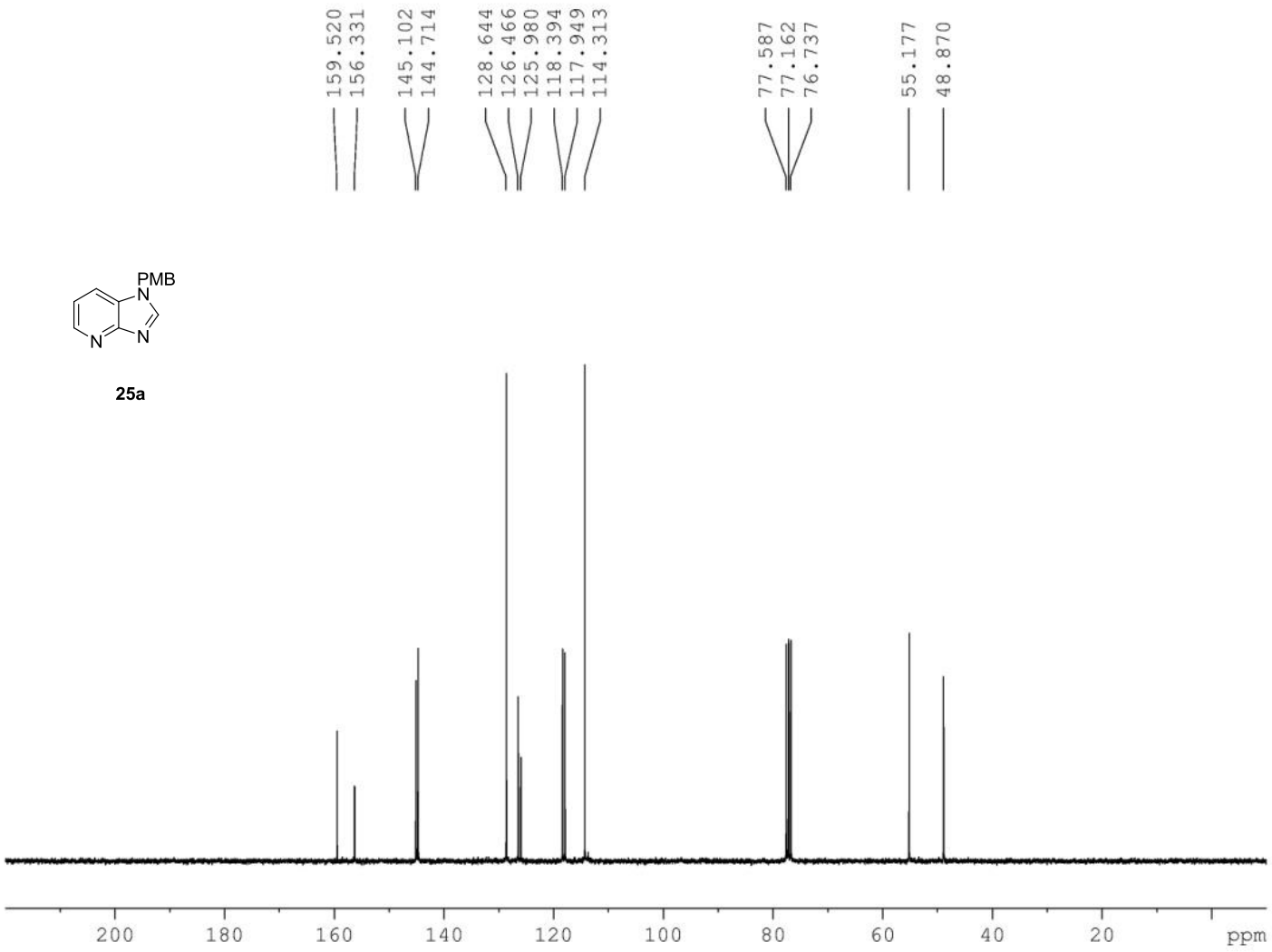
151.237
140.737
134.669
130.292
77.583
77.160
76.736
41.209
31.452
20.225
13.907
200
180
160
140
120
100
80
60
40
20
ppm


8.573
8.568
8.558
8.553
8.155
7.599
7.594
7.572
7.567
7.260
7.187
7.171
7.160
7.157
7.150
7.144
7.128
6.894
6.865
5.304
3.795
1.754

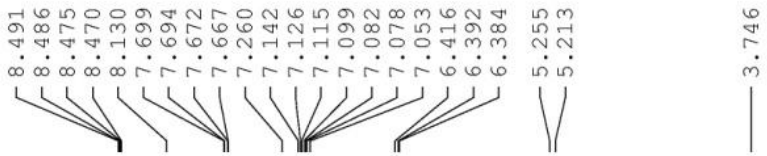

PMB
N
N
N

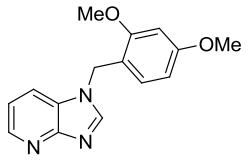
25a


9
8
7
6
5
4
3
2
1
ppm
0.89
0.88
0.94
2.85
1.99
2.00
3.03

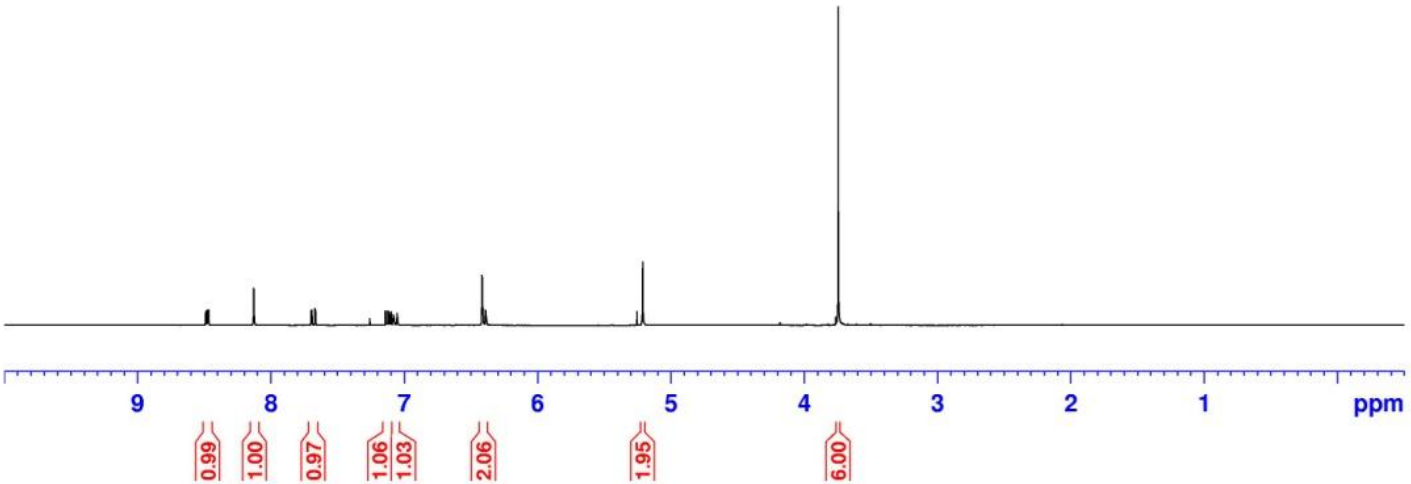

159.520
156.331
145.102
144.714
128.644
126.466
125.980
118.394
117.949
114.313
77.587
77.162
76.737
55.177
48.870
PMB
N
N
N
200
180
160
140
120
100
80
60
40
20
ppm

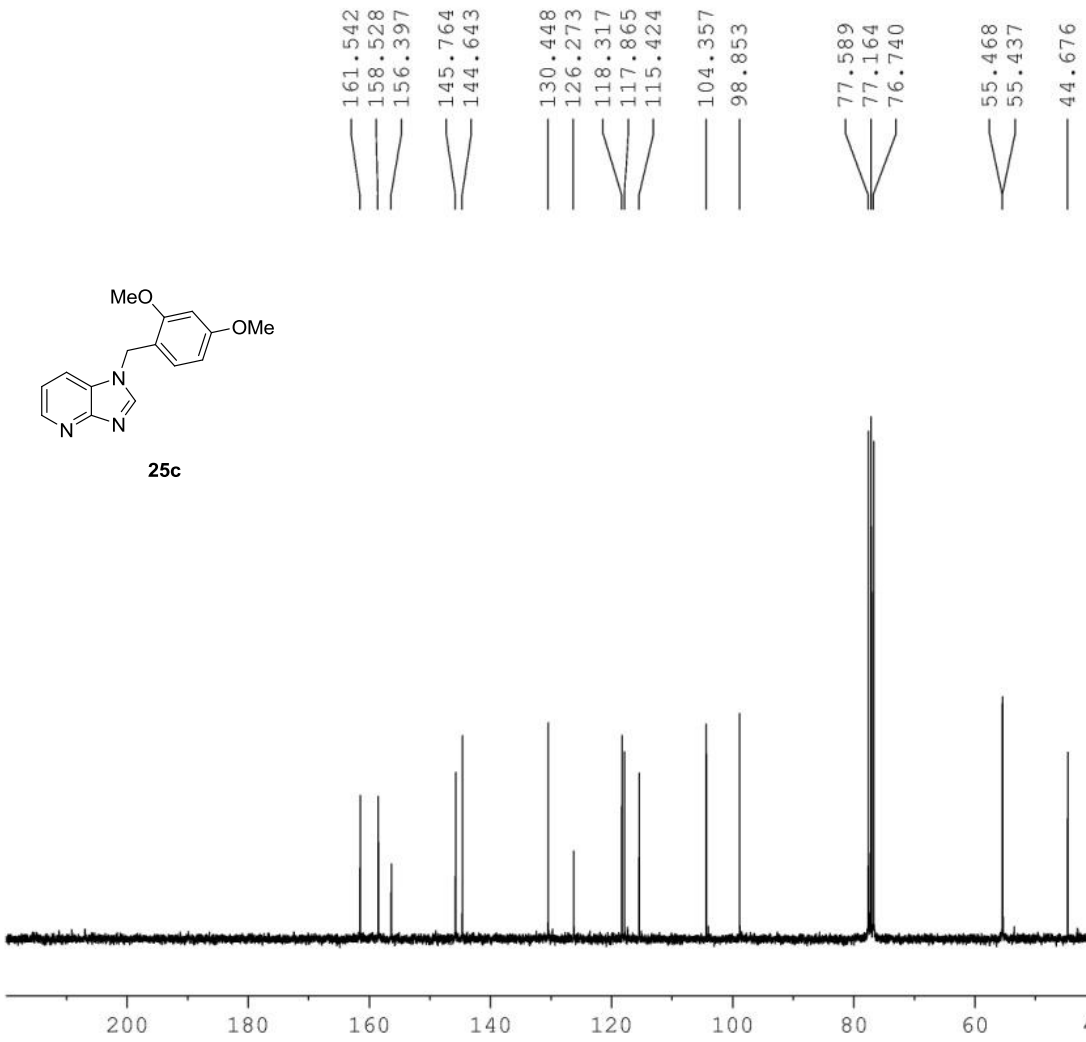
25a


8.491
8.486
8.475
8.470
8.130
7.699
7.694
7.672
7.667
7.260
7.142
7.126
7.115
7.099
7.082
7.078
7.053
6.416
6.392
6.384
5.255
5.213
3.746

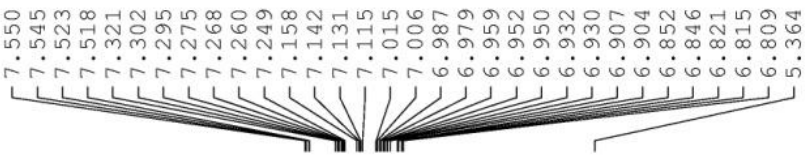

MeO
OMe
N
N
N

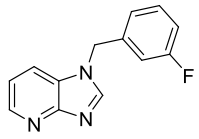
25c


9
8
7
6
5
4
3
2
1
ppm
0.99
1.00
0.97
1.06
1.03
2.06
1.95
6.00

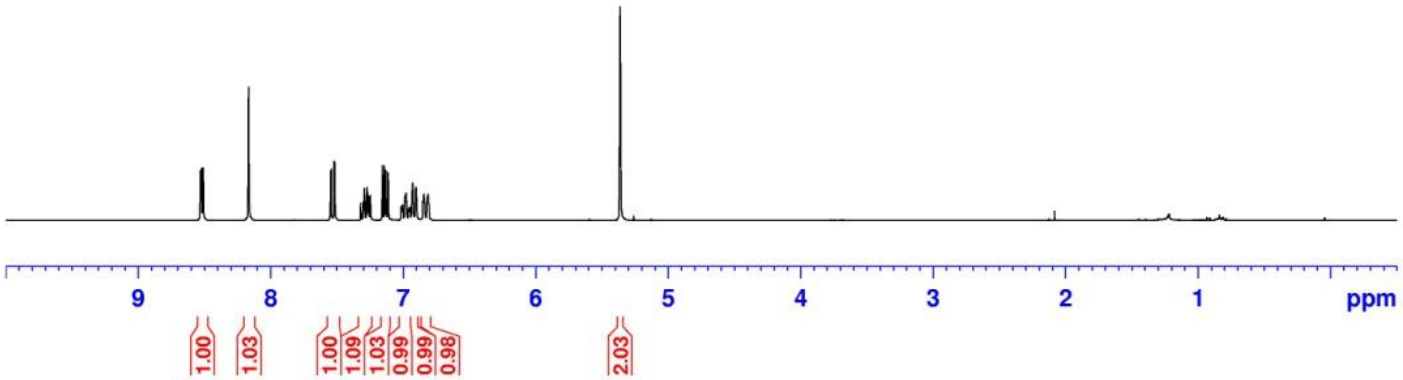

161.542
158.528
156.397
145.764
144.643
130.448
126.273
118.317
117.865
115.424
104.357
98.853
77.589
77.164
76.740
55.468
55.437
44.676
MeO
OMe
N
N
N
200
180
160
140
120
100
80
60
40
20
ppm

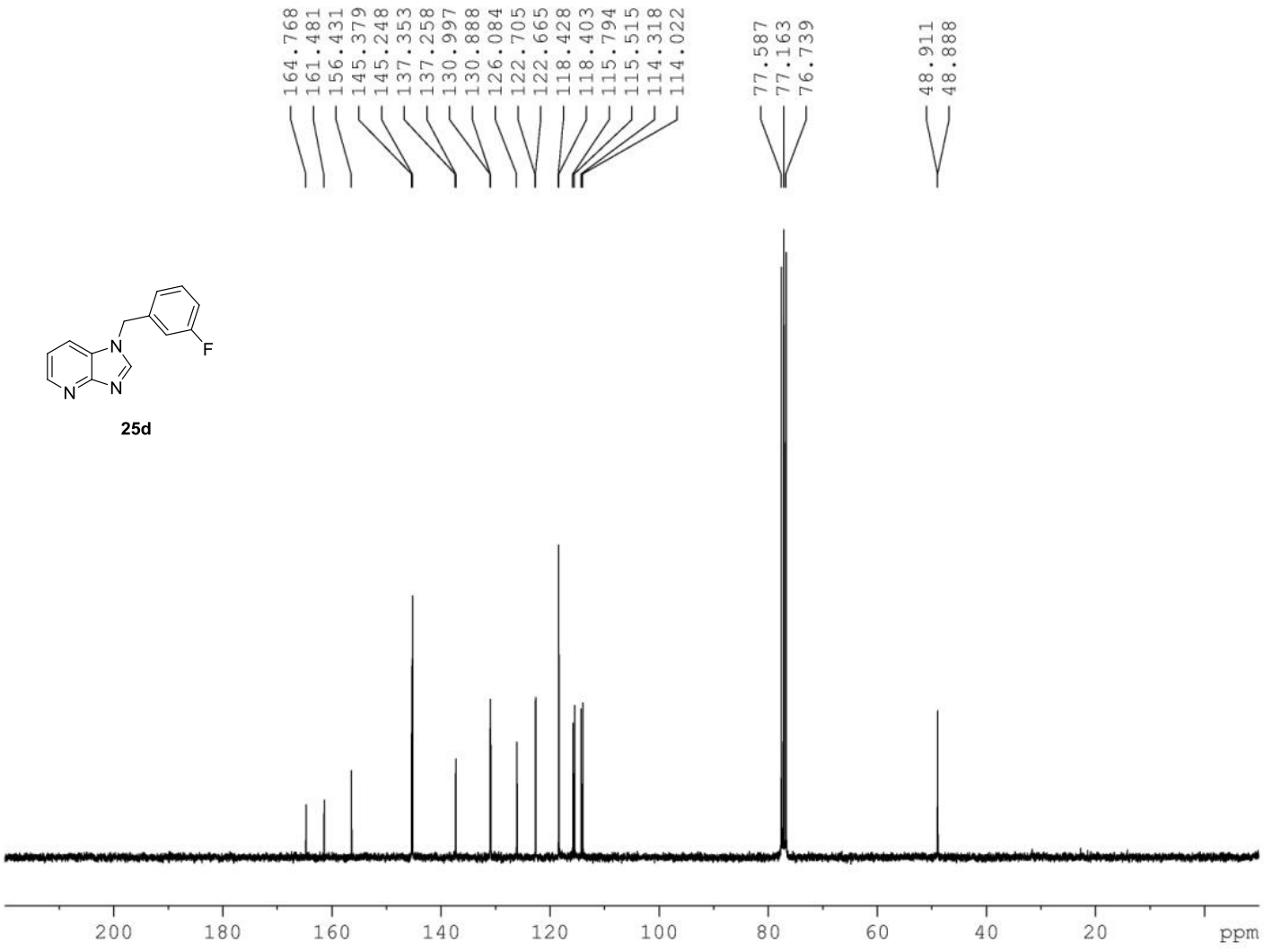
25c

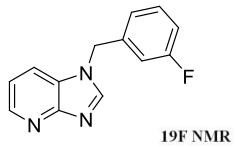

7.550
7.545
7.523
7.518
7.321
7.302
7.295
7.275
7.268
7.260
7.249
7.158
7.142
7.131
7.115
7.015
7.006
6.987
6.979
6.959
6.952
6.950
6.932
6.930
6.907
6.904
6.852
6.846
6.821
6.815
6.809
5.364


N
F
N
N

25d

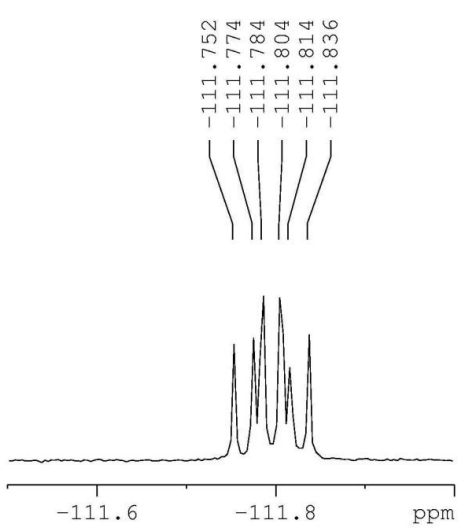

9
8
7
6
5
4
3
2
1
ppm
1.00
1.03
1.00
1.09
1.03
0.99
0.99
0.98
2.03


164.768
161.481
156.431
145.379
145.248
137.353
137.258
130.997
130.888
126.084
122.705
122.665
118.428
118.403
115.794
115.515
114.318
114.022
77.587
77.163
76.739
48.911
48.888
F
N
N
N
25d
200
180
160
140
120
100
80
60
40
20
ppm



19F NMR

25d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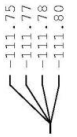
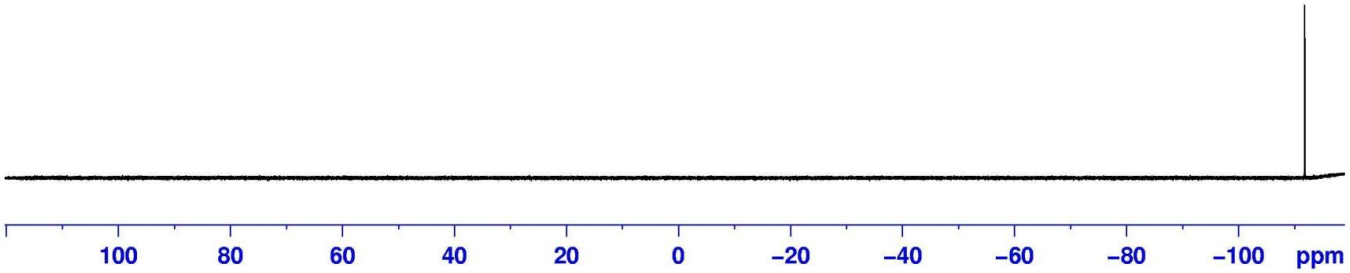
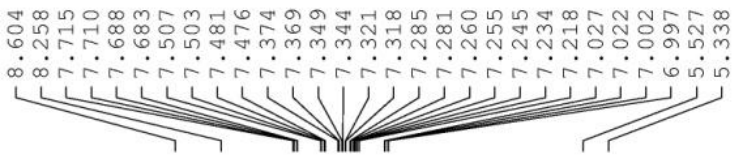
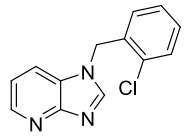
-111.774
-111.784
-111.804
-111.814
-111.836
-111.6
-111.8
ppm

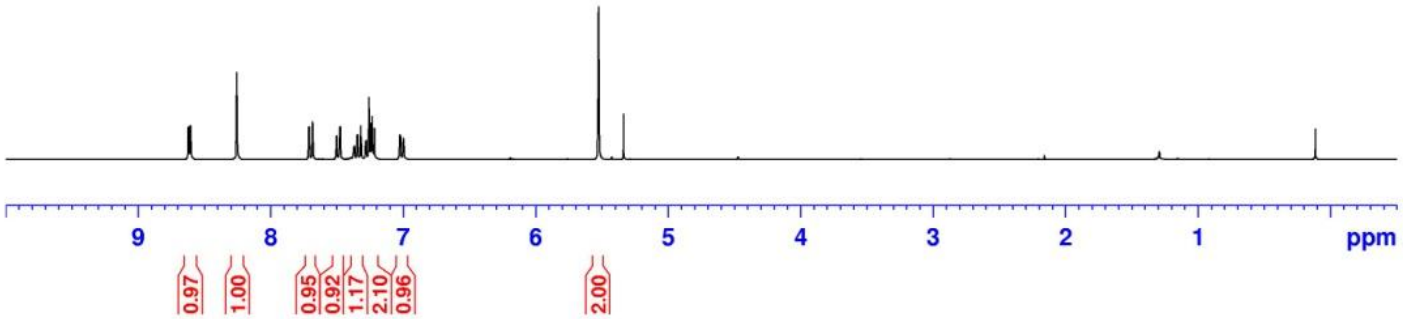

-111.75
-111.77
-111.78
-111.80

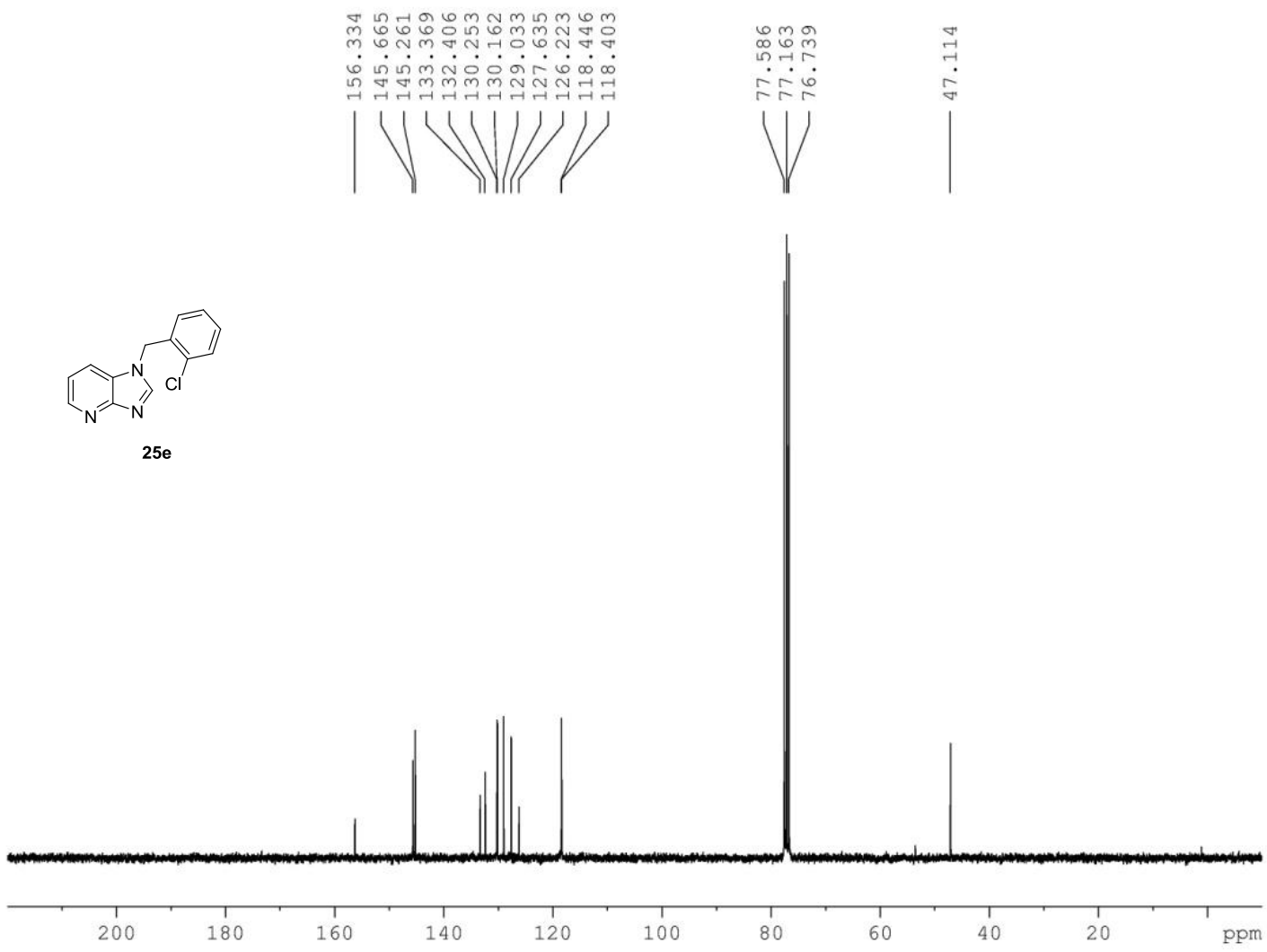

100
80
60
40
20
0
-20
-40
-60
-80
-100
ppm


8.604
8.258
7.715
7.710
7.688
7.683
7.507
7.503
7.481
7.476
7.374
7.369
7.349
7.344
7.321
7.318
7.285
7.281
7.260
7.255
7.245
7.234
7.218
7.027
7.022
7.002
6.997
5.527
5.338

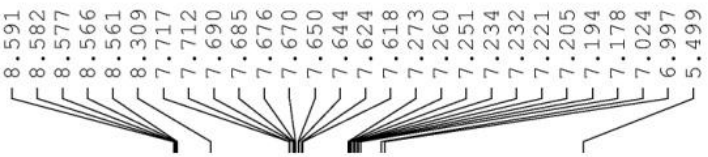

N
Cl
N
N

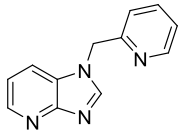
25e


9
8
7
6
5
4
3
2
1
ppm
0.97
1.00
0.95
0.92
1.17
2.10
0.96
2.00

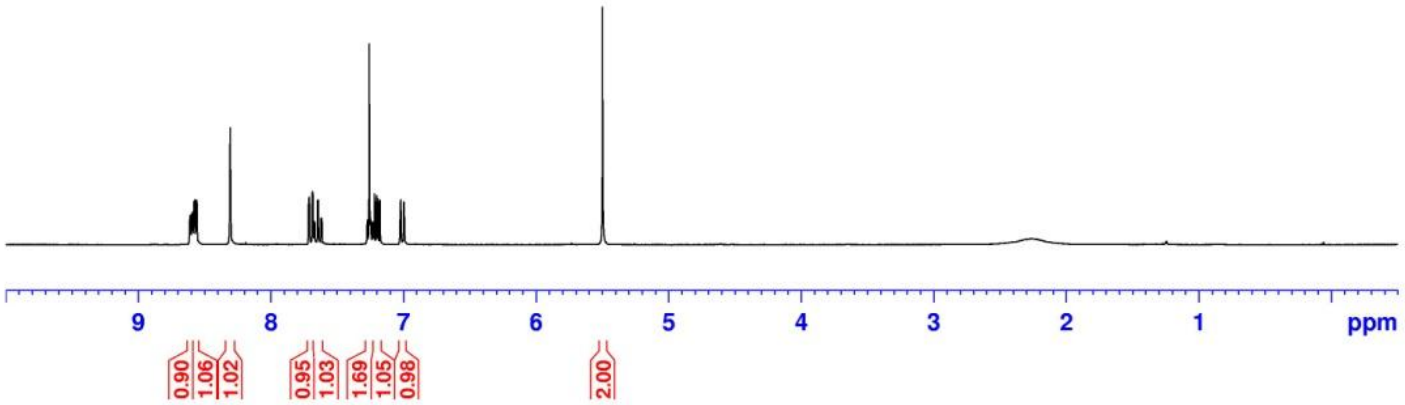

156.334
145.665
145.261
133.369
132.406
130.253
130.162
129.033
127.635
126.223
118.446
118.403
77.586
77.163
76.739
47.114
N
Cl
N
N
200
180
160
140
120
100
80
60
40
20
ppm

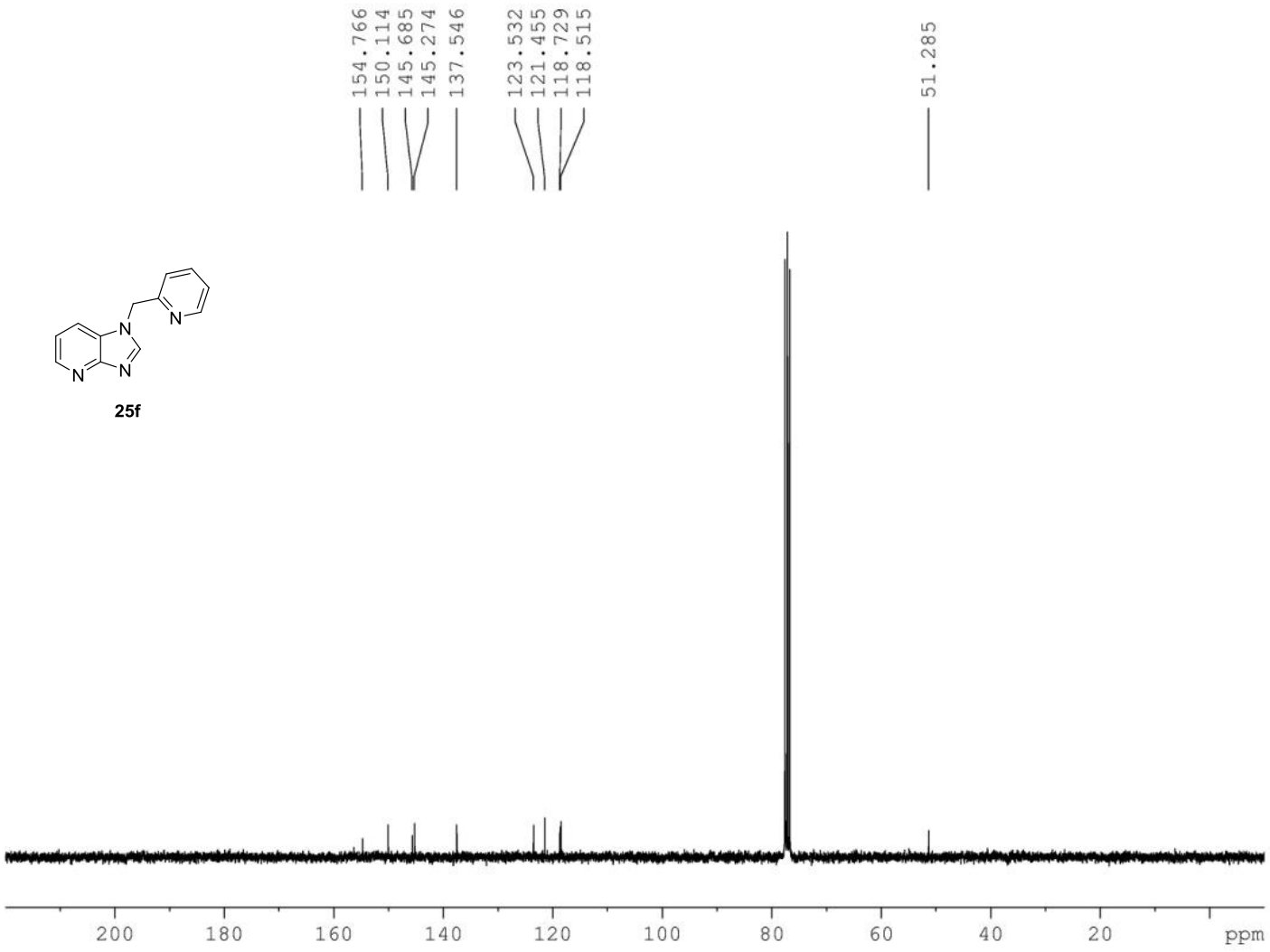
25e


8.591
8.582
8.577
8.566
8.561
8.309
7.717
7.712
7.690
7.685
7.676
7.670
7.650
7.644
7.624
7.618
7.273
7.260
7.251
7.234
7.232
7.221
7.205
7.194
7.178
7.024
6.997
5.499

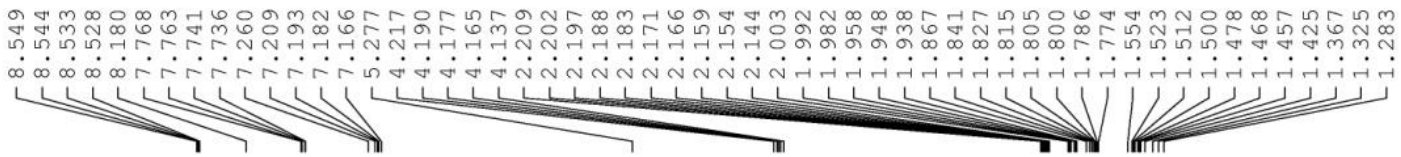


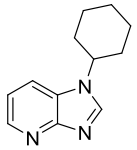
25f


9
8
7
6
5
4
3
2
1
ppm
0.90
1.06
1.02
0.95
1.03
1.69
1.05
0.98
2.00

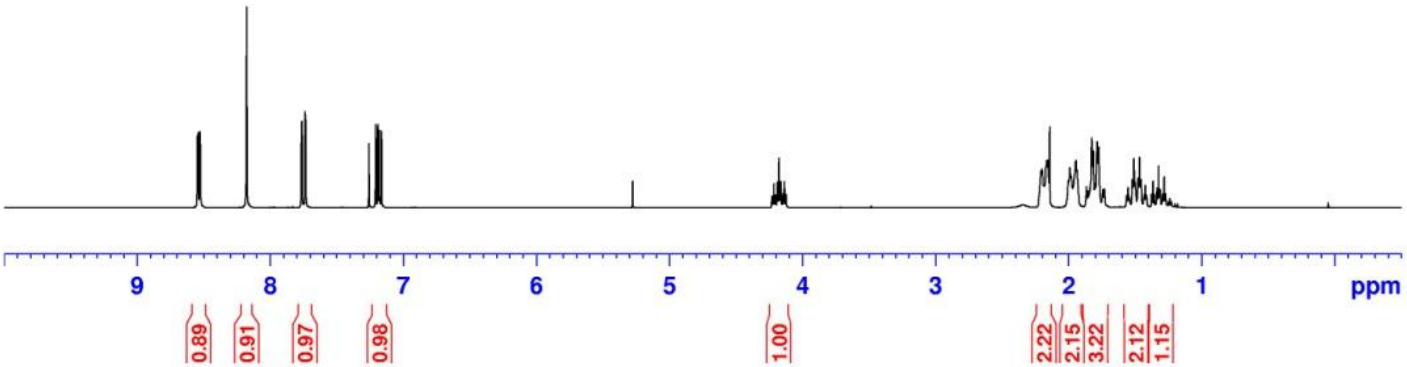

154.766
150.114
145.685
145.274
137.546
123.532
121.455
118.729
118.515
51.285
N
N
N
200
180
160
140
120
100
80
60
40
20
ppm

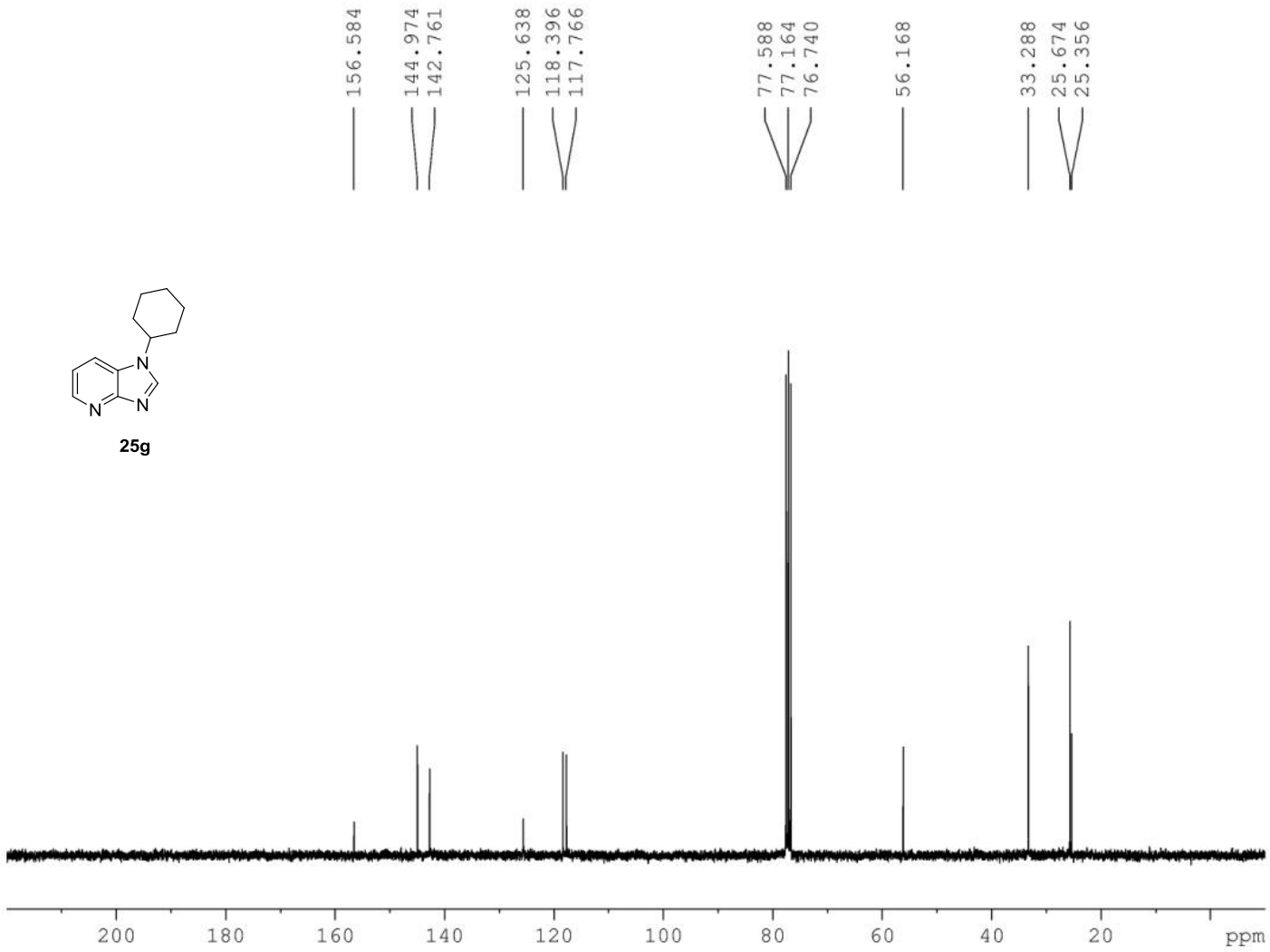
25f


8.549
8.544
8.533
8.528
8.180
7.768
7.763
7.741
7.736
7.260
7.209
7.193
7.182
7.166
5.277
4.217
4.190
4.177
4.165
4.137
2.209
2.202
2.197
2.188
2.183
2.171
2.166
2.159
2.154
2.144
2.003
1.992
1.982
1.958
1.948
1.938
1.867
1.841
1.827
1.815
1.805
1.800
1.786
1.774
1.554
1.523
1.512
1.500
1.478
1.468
1.457
1.425
1.367
1.325
1.283

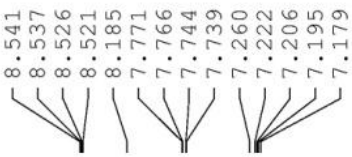

N
N
N

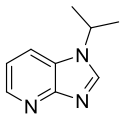
25g


9
8
7
6
5
4
3
2
1
ppm
0.89
0.91
0.97
0.98
1.00
2.22
2.15
3.22
2.12
1.15

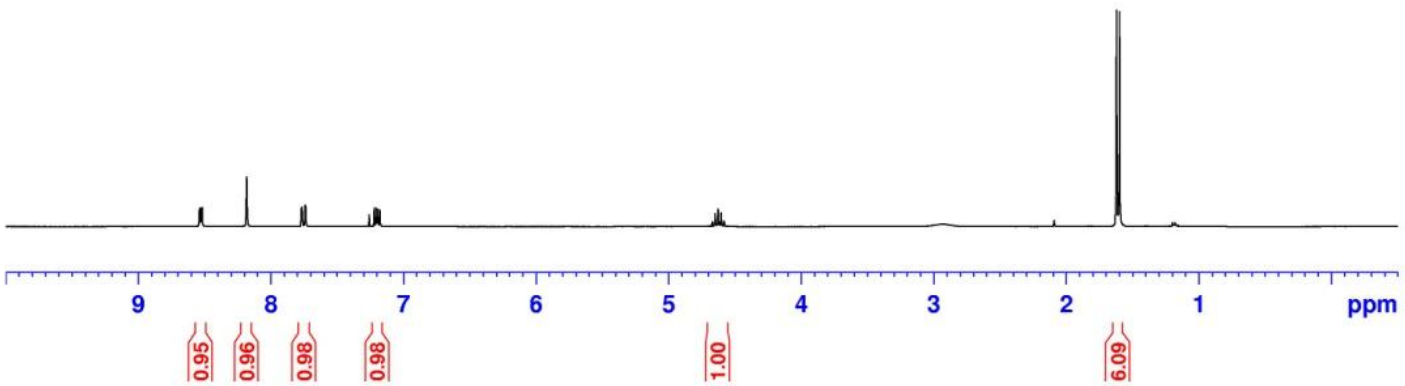

156.584
144.974
142.761
125.638
118.396
117.766
77.588
77.164
76.740
56.168
33.288
25.674
25.356
N
N
N
200
180
160
140
120
100
80
60
40
20
ppm

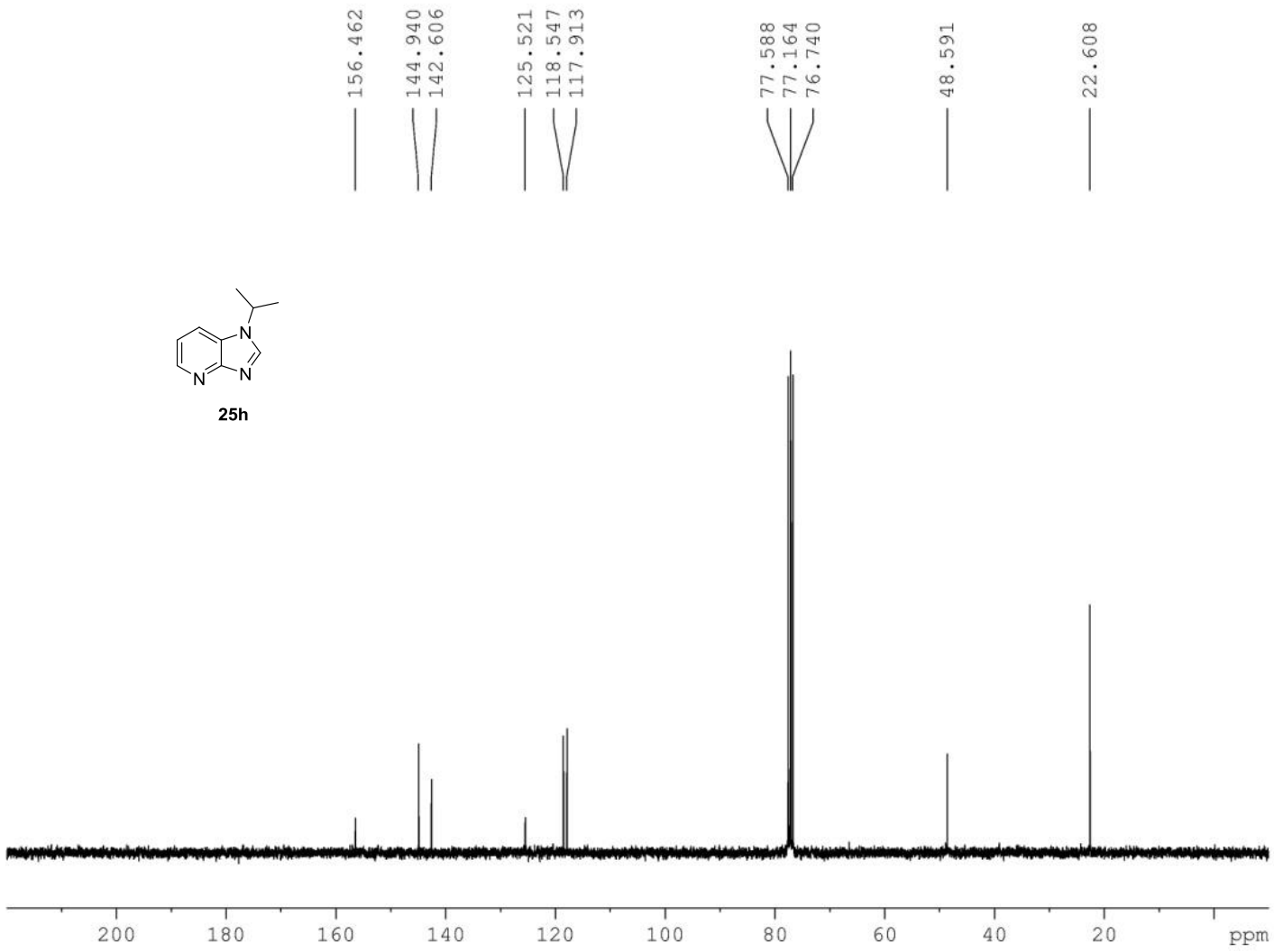
25g


8.541
8.537
8.526
8.521
8.185
7.771
7.766
7.744
7.739
7.260
7.222
7.206
7.195
7.179
4.695
4.673
4.650
4.628
4.605
4.583
4.560
1.622
1.600

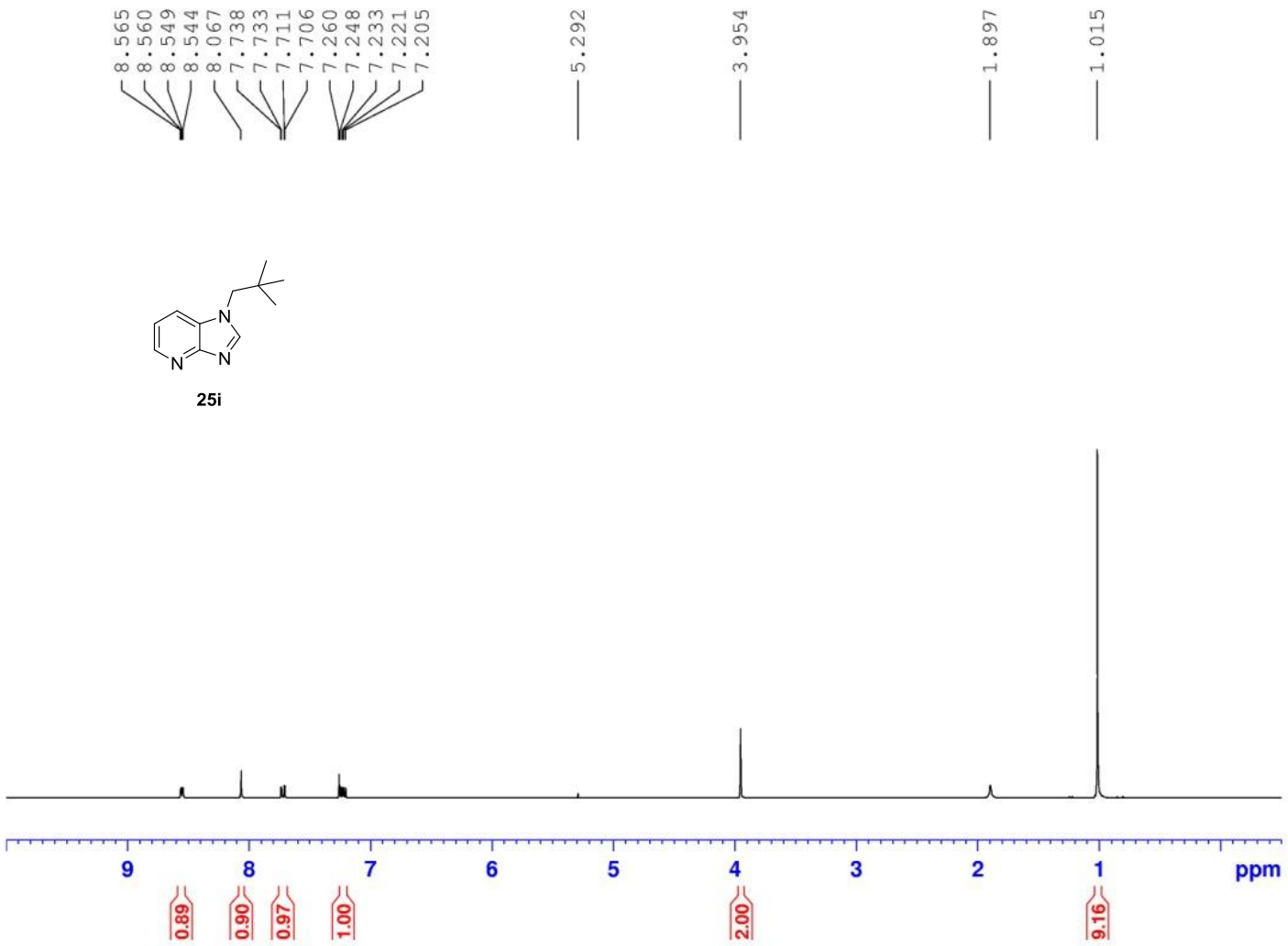


25h

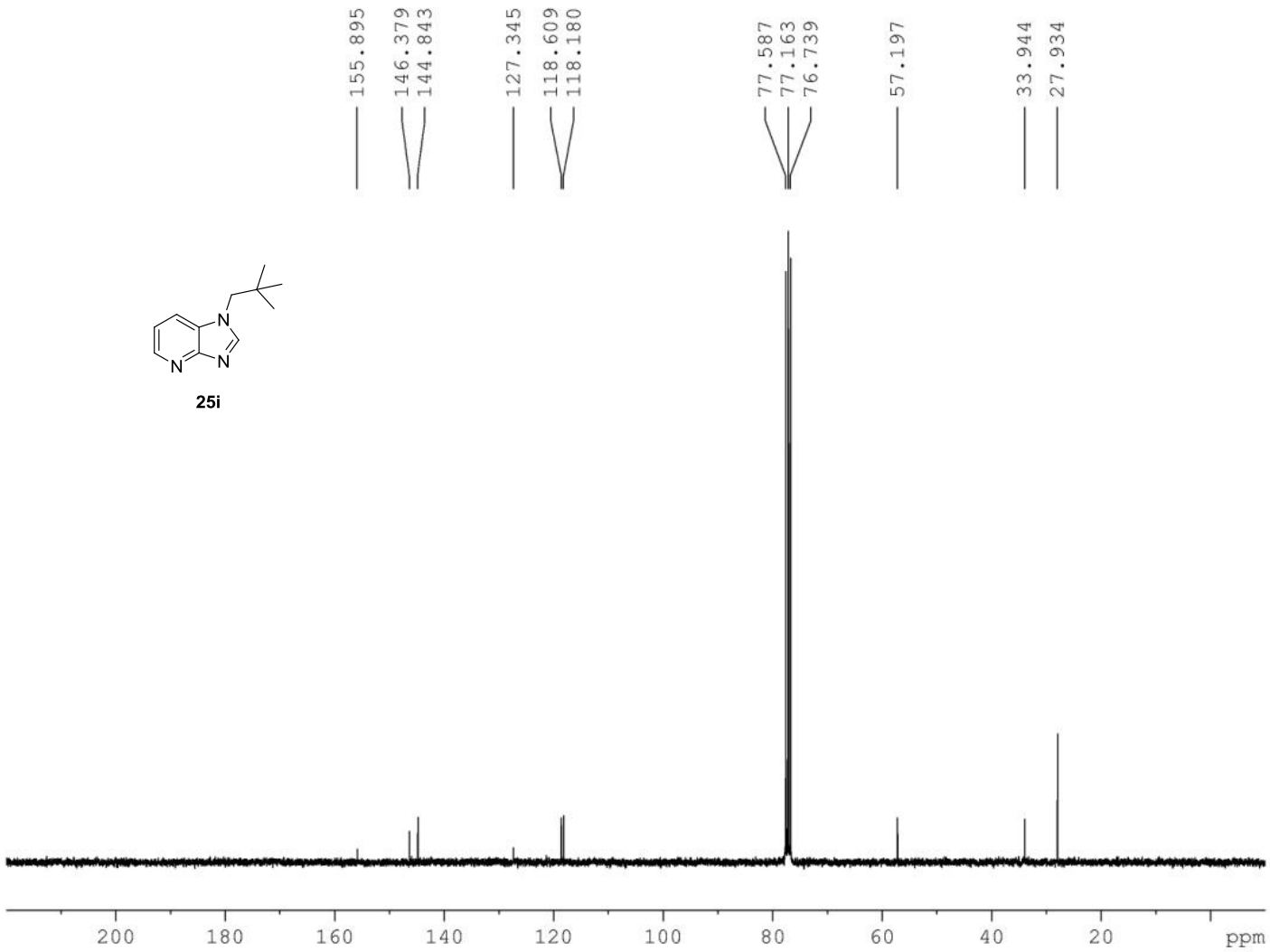

9
8
7
6
5
4
3
2
1
ppm
0.95
0.96
0.98
0.98
1.00
6.09


156.462
144.940
142.606
125.521
118.547
117.913
77.588
77.164
76.740
48.591
22.608
N
N
N
200
180
160
140
120
100
80
60
40
20
ppm

25h


8.565
8.560
8.549
8.544
8.067
7.738
7.733
7.711
7.706
7.260
7.248
7.233
7.221
7.205
5.292
3.954
1.897
1.015
N
N
N
9
8
7
6
5
4
3
2
1
ppm
0.89
0.90
0.97
1.00
2.00
9.16

25i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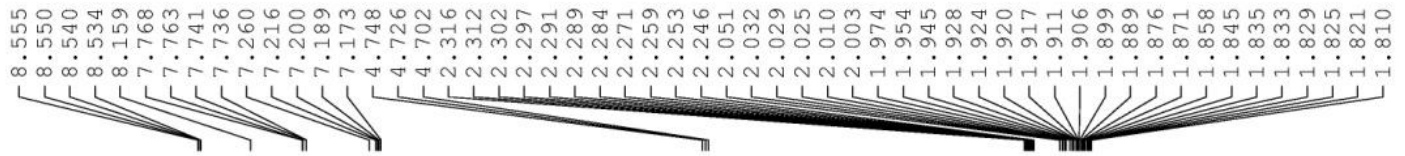
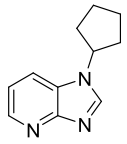
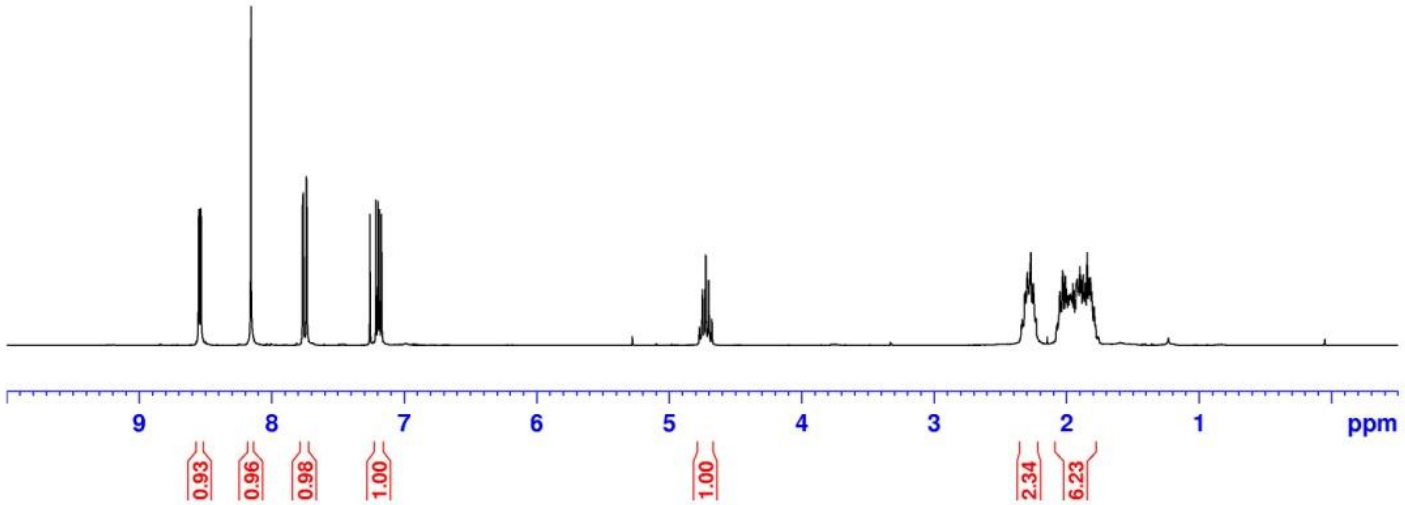
146.379
144.843
127.345
118.609
118.180
77.587
77.163
76.739
57.197
33.944
27.934
N
N
N
200
180
160
140
120
100
80
60
40
20
ppm

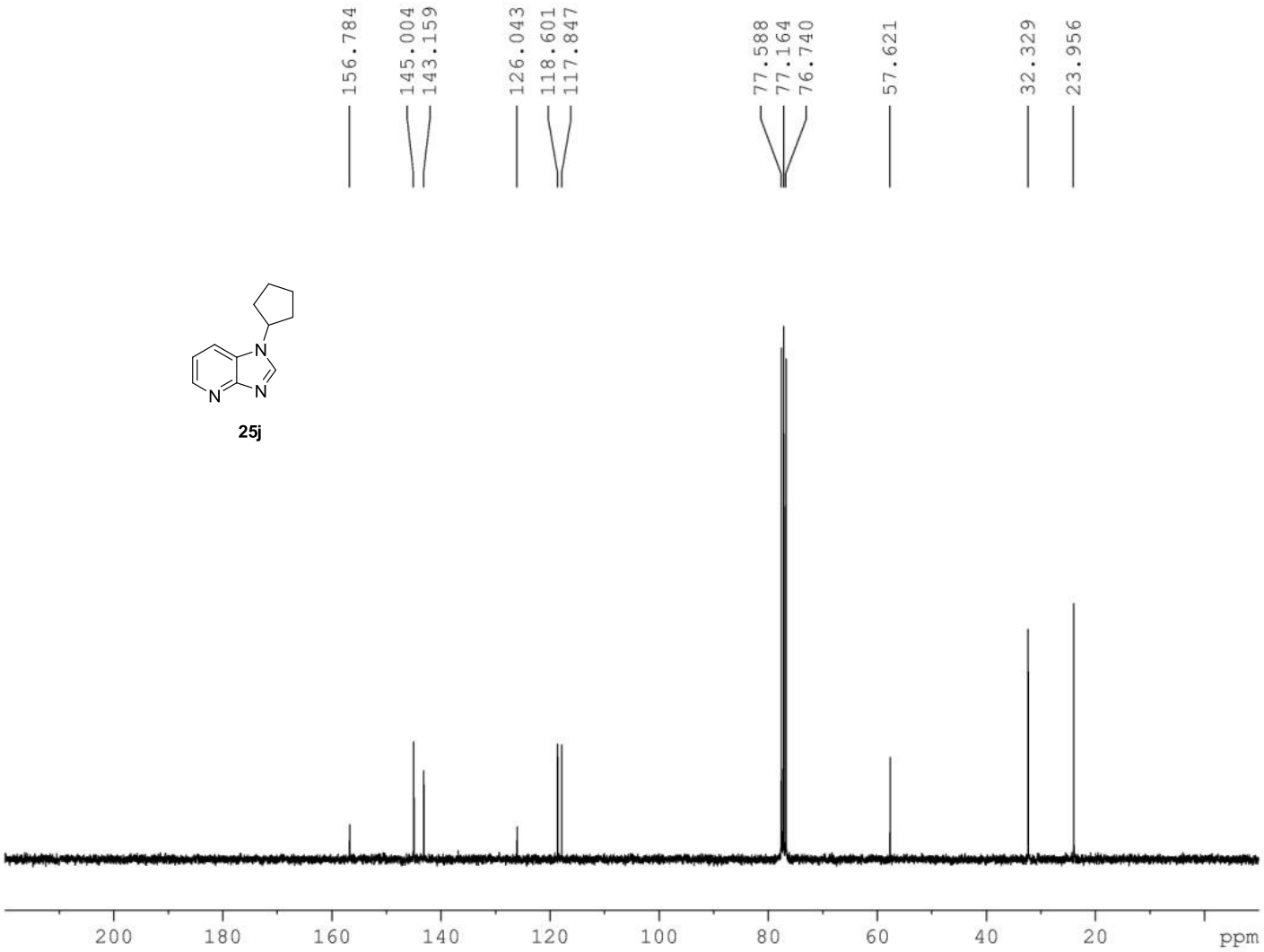
25i


8.555
8.550
8.540
8.534
8.159
7.768
7.763
7.741
7.736
7.260
7.216
7.200
7.189
7.173
4.748
4.726
4.702
2.316
2.312
2.302
2.297
2.291
2.289
2.284
2.271
2.259
2.253
2.246
2.051
2.032
2.029
2.025
2.010
2.003
1.974
1.954
1.945
1.928
1.924
1.920
1.917
1.911
1.906
1.899
1.889
1.876
1.871
1.858
1.845
1.835
1.833
1.829
1.825
1.821
1.810


N
N
N

25j


9
8
7
6
5
4
3
2
1
ppm
0.93
0.96
0.98
1.00
1.00
2.34
6.23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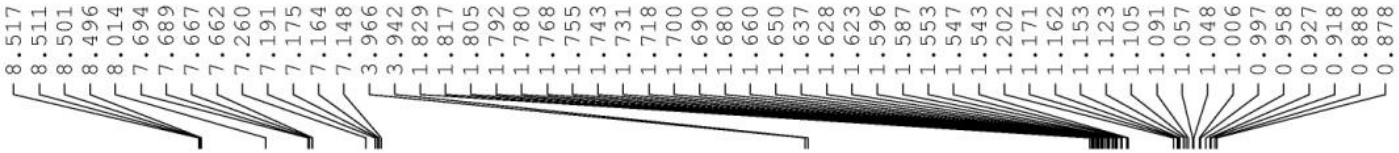
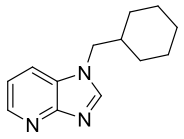
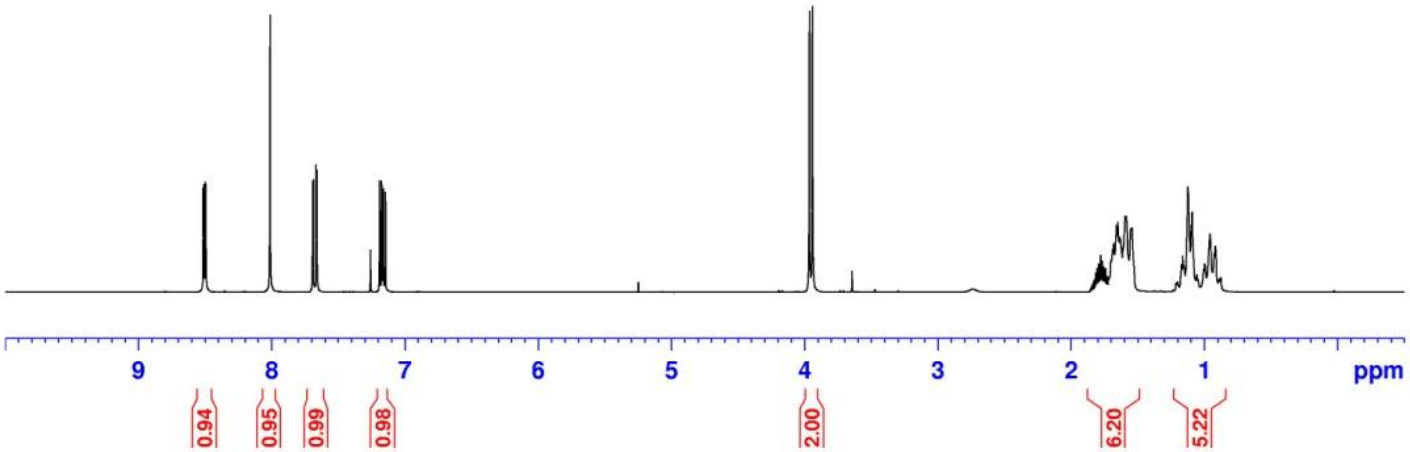
145.004
143.159
126.043
118.601
117.847
77.588
77.164
76.740
57.621
32.329
23.956
N
N
N
200
180
160
140
120
100
80
60
40
20
ppm

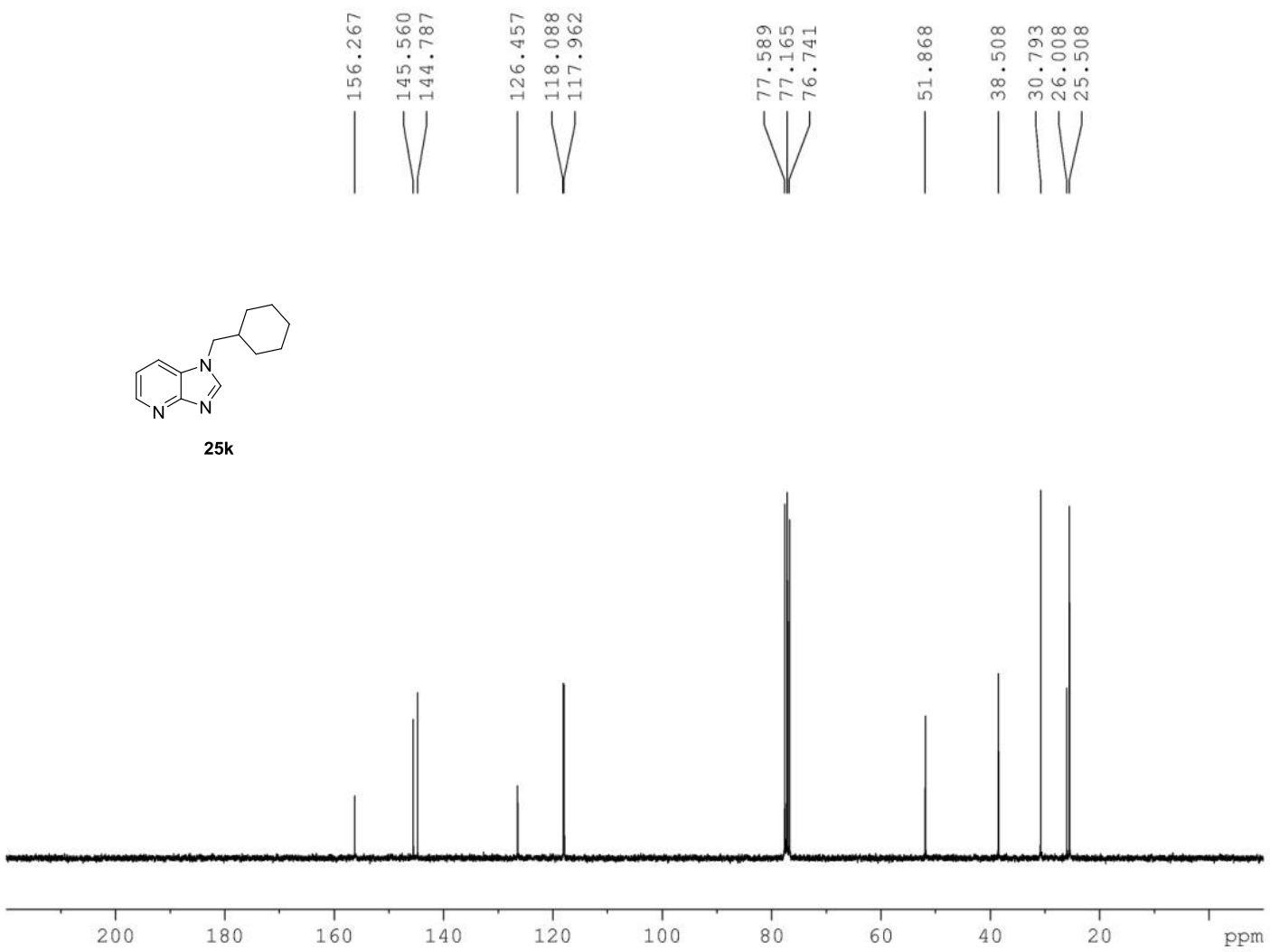
25j


8.517
8.511
8.501
8.496
8.014
7.694
7.689
7.667
7.662
7.260
7.191
7.175
7.164
7.148
3.966
3.942
1.829
1.817
1.805
1.792
1.780
1.768
1.755
1.743
1.731
1.718
1.700
1.690
1.680
1.660
1.650
1.637
1.628
1.623
1.596
1.587
1.553
1.547
1.543
1.202
1.171
1.162
1.153
1.123
1.105
1.091
1.057
1.048
1.006
0.997
0.958
0.927
0.918
0.888
0.878


N
N
N

25k


9
8
7
6
5
4
3
2
1
ppm
0.94
0.95
0.99
0.98
2.00
6.20
5.22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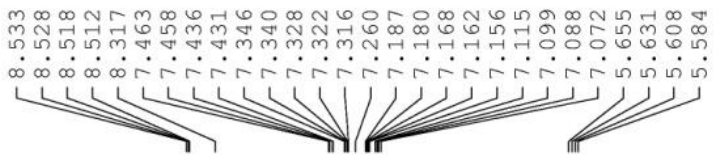
145.560
144.787
126.457
118.088
117.962
77.589
77.165
76.741
51.868
38.508
30.793
26.008
25.508
N
N
N
25k
200
180
160
140
120
100
80
60
40
20
ppm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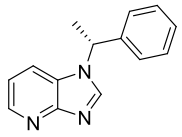
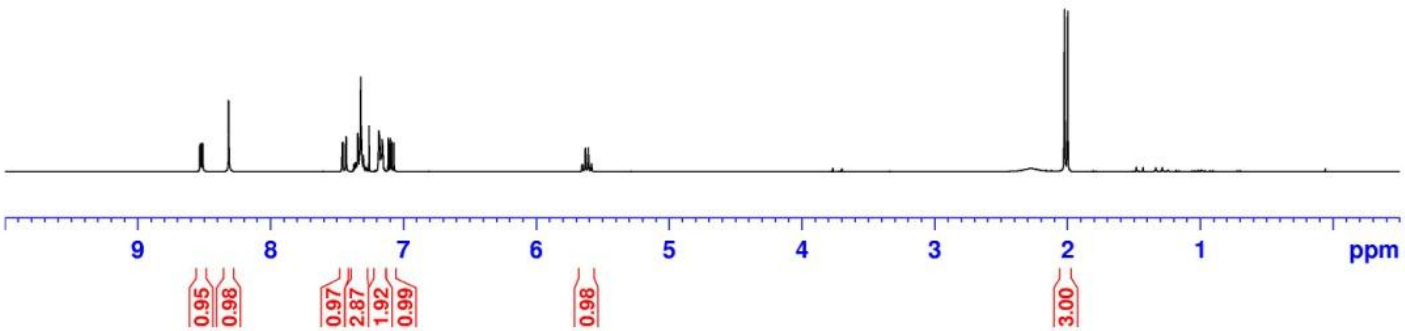
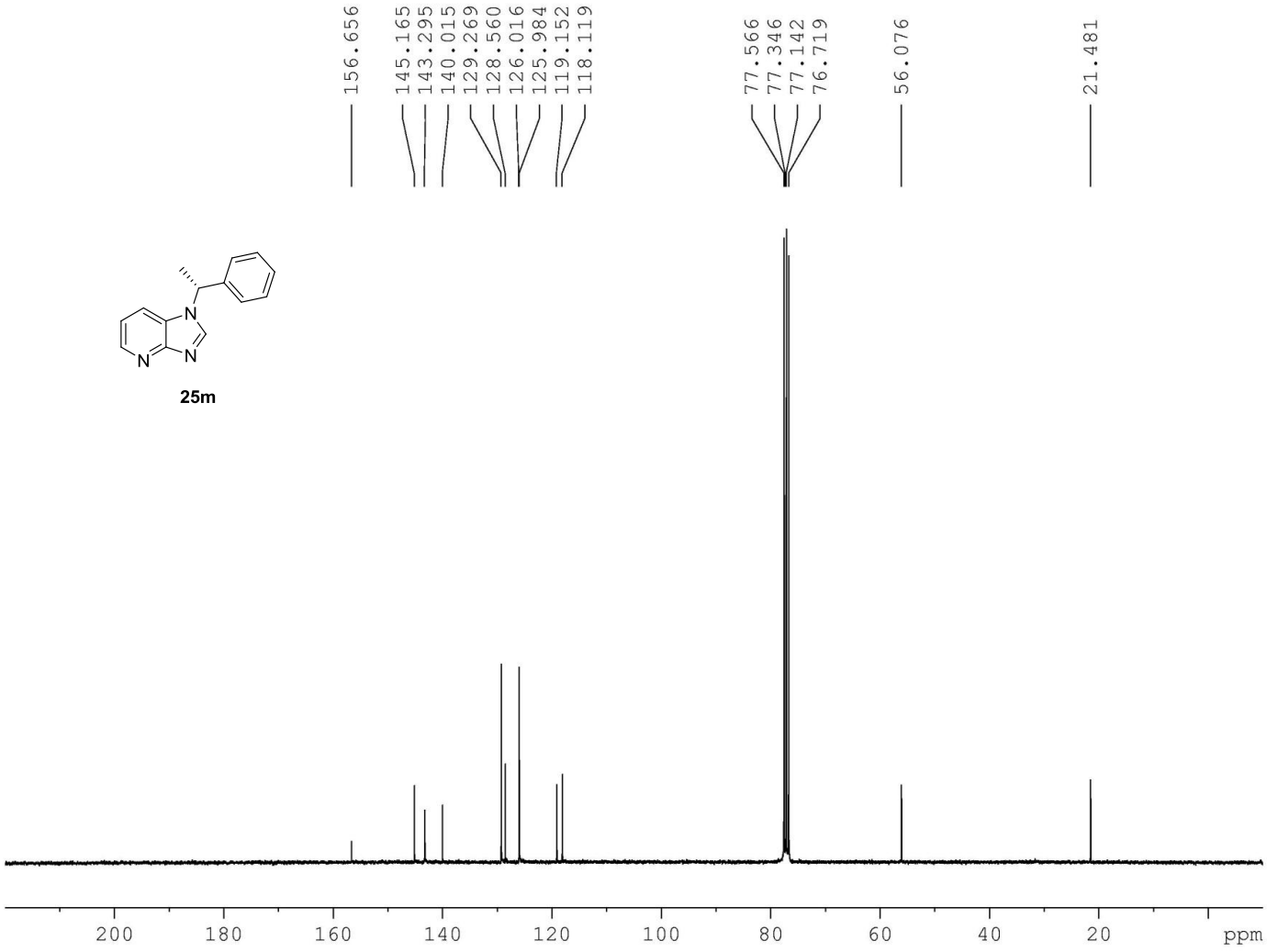
8.528
8.518
8.512
8.317
7.463
7.458
7.436
7.431
7.346
7.340
7.328
7.322
7.316
7.260
7.187
7.180
7.168
7.162
7.156
7.115
7.099
7.088
7.072
5.655
5.631
5.608
5.584
2.023
2.000



25m


9
8
7
6
5
4
3
2
1
ppm
0.95
0.98
0.97
2.87
1.92
0.99
0.98
3.00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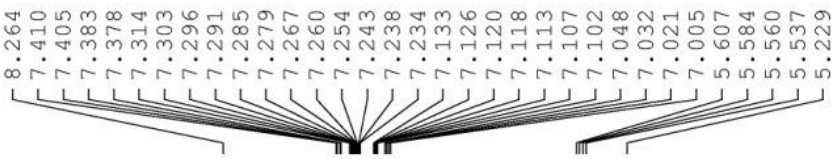
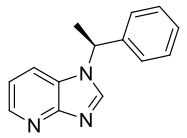
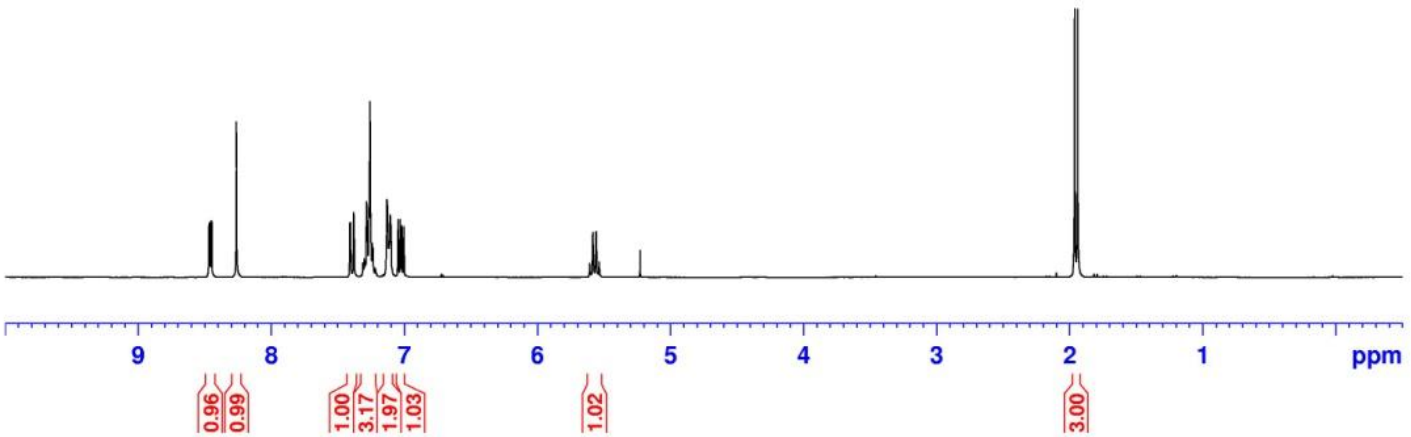
145.165
143.295
140.015
129.269
128.560
126.016
125.984
119.152
118.119
77.566
77.346
77.142
76.719
56.076
21.481
200
180
160
140
120
100
80
60
40
20
ppm

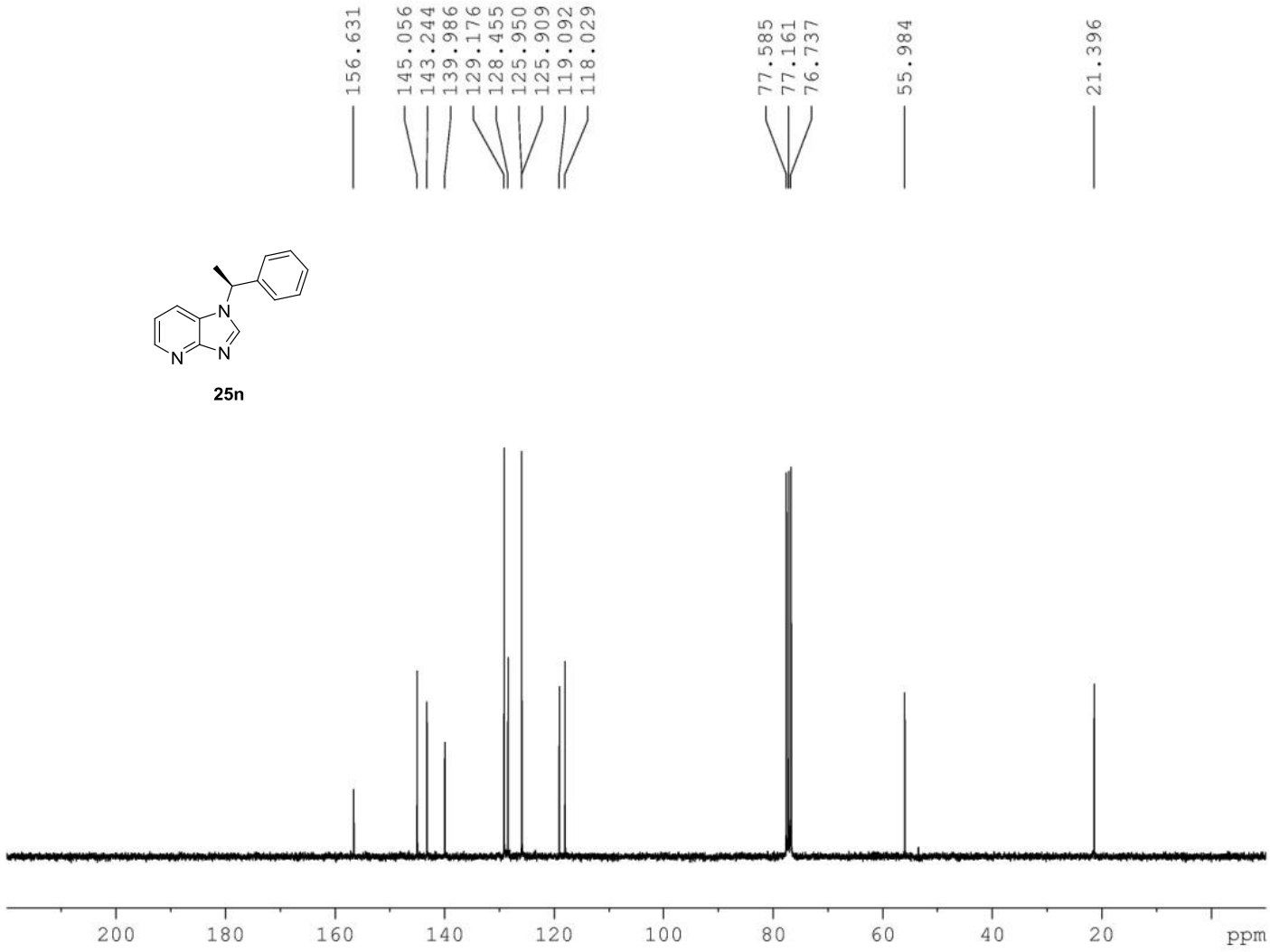
25m


8.264
7.410
7.405
7.383
7.378
7.314
7.303
7.296
7.291
7.285
7.279
7.267
7.260
7.254
7.243
7.238
7.234
7.133
7.126
7.120
7.118
7.113
7.107
7.102
7.048
7.032
7.021
7.005
5.607
5.584
5.560
5.537
5.229
1.963
1.940



25n


9
8
7
6
5
4
3
2
1
ppm
0.96
0.99
1.00
3.17
1.97
1.03
1.02
3.00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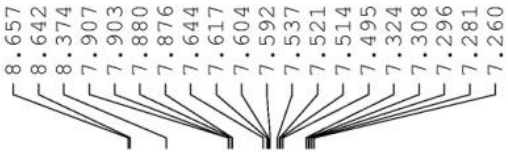
143.244
139.986
129.176
128.455
125.950
125.909
119.092
118.029
77.585
77.161
76.737
55.984
21.396
N
N
N
200
180
160
140
120
100
80
60
40
20
ppm

25n


8.657
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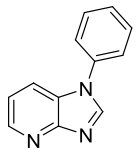
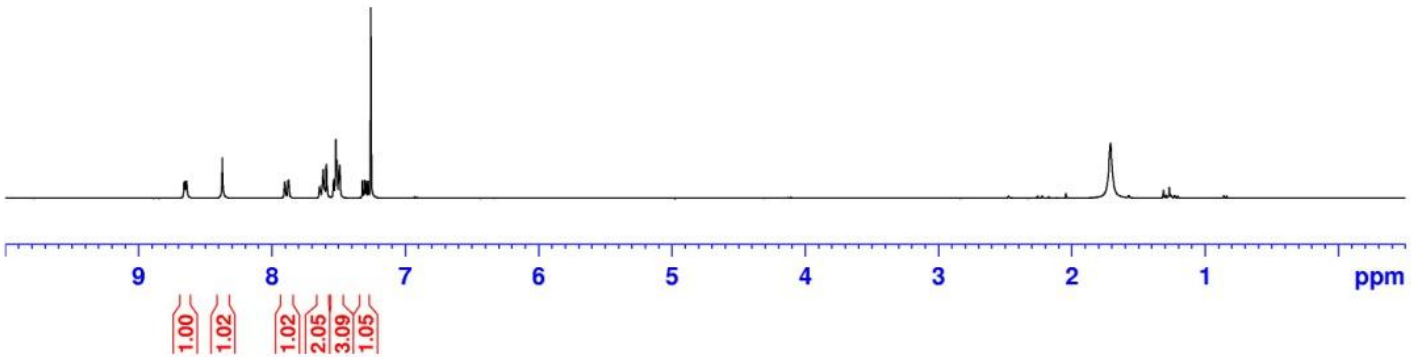
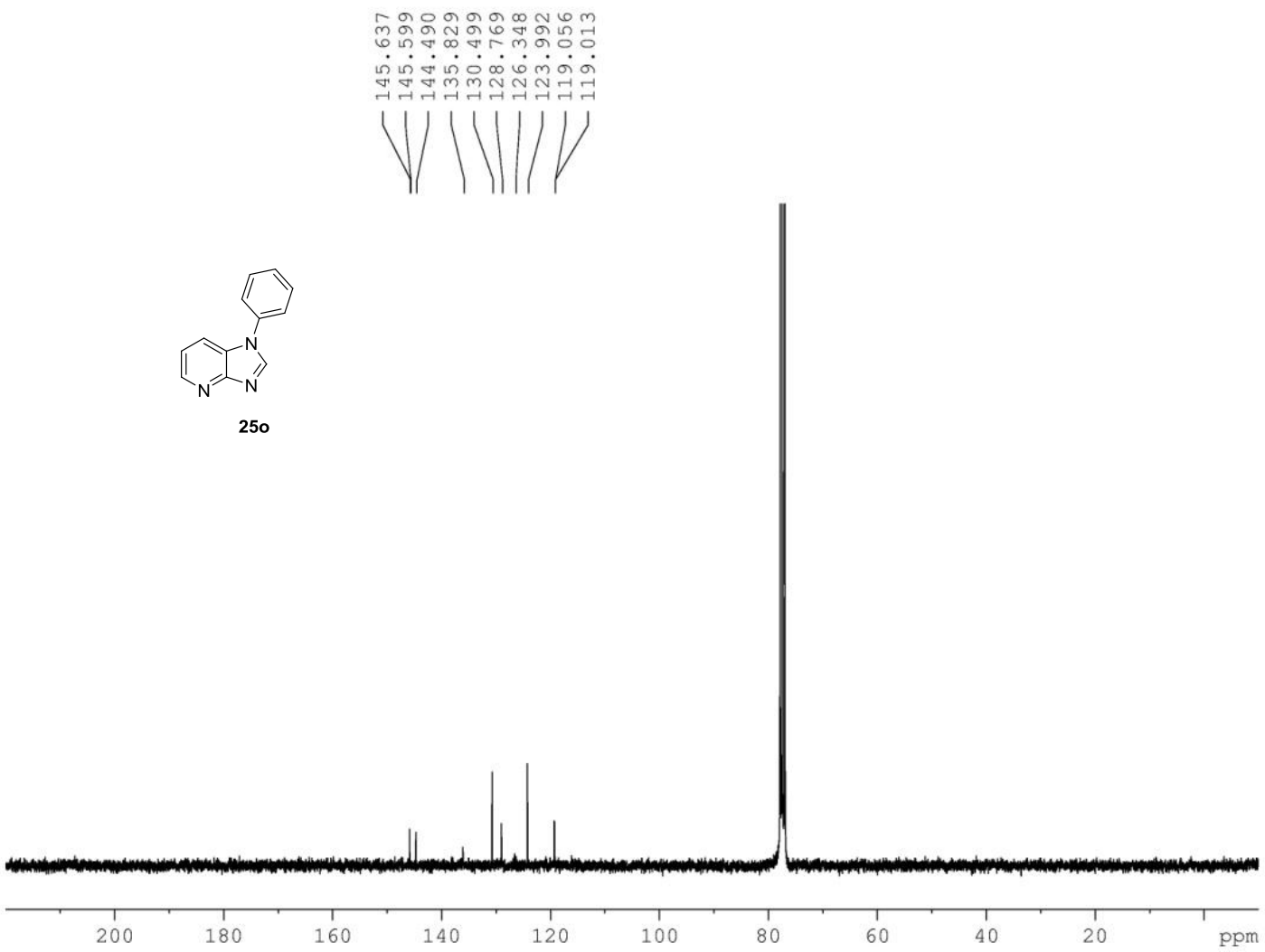
8.374
7.907
7.903
7.880
7.876
7.644
7.617
7.604
7.592
7.537
7.521
7.514
7.495
7.324
7.308
7.296
7.281
7.260


1.711

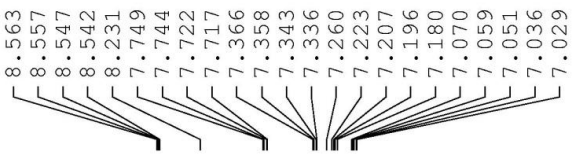

N
N
N

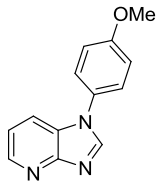
25o


9
8
7
6
5
4
3
2
1
ppm
1.00
1.02
1.02
2.05
3.09
1.05

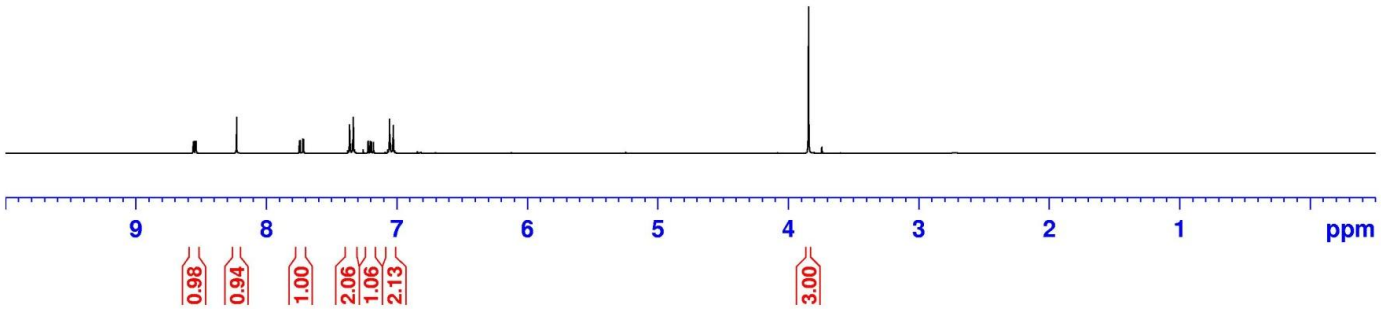

145.637
145.599
144.490
135.829
130.499
128.769
126.348
123.992
119.056
119.013
N
N
N
200
180
160
140
120
100
80
60
40
20
ppm

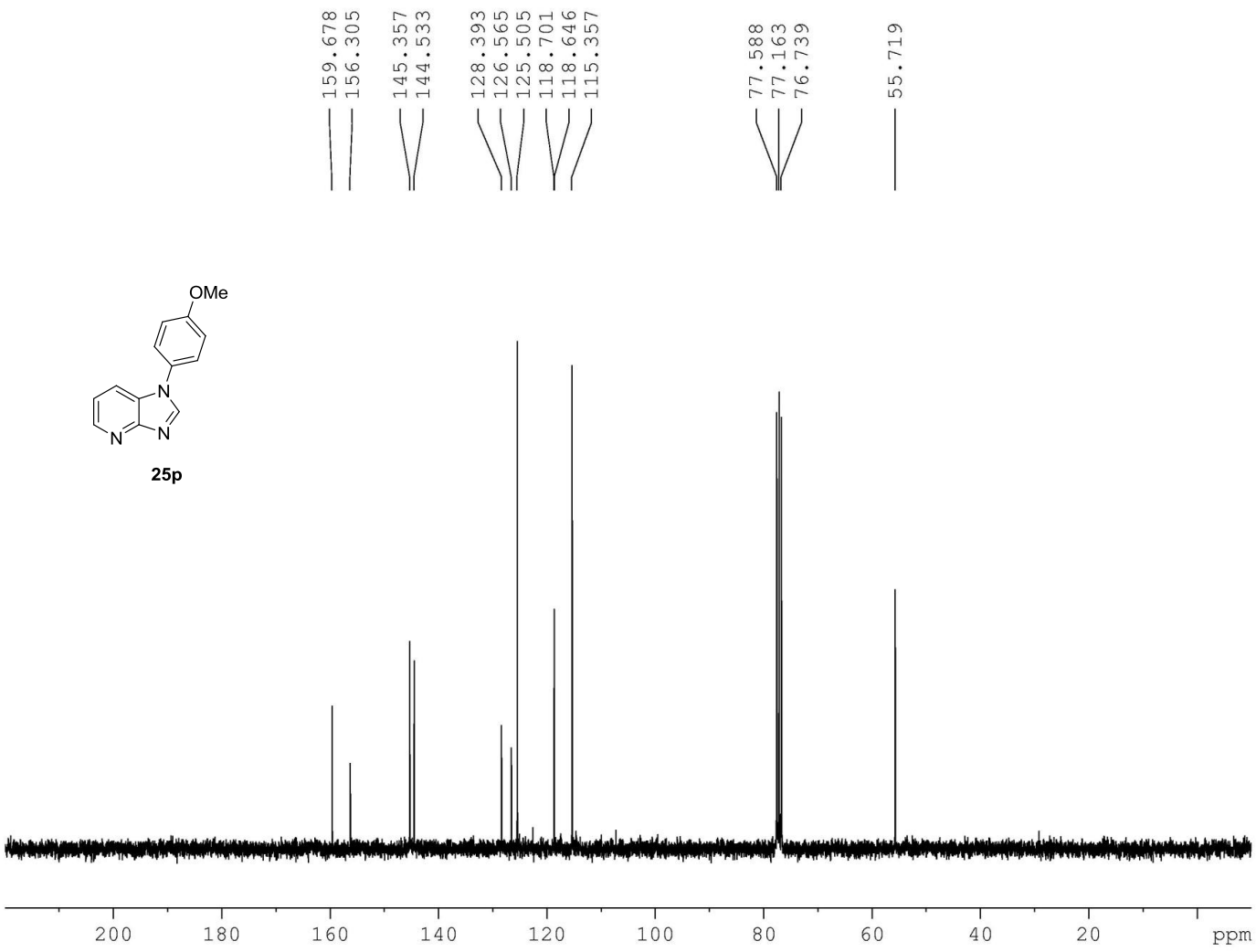
25o


8.563
8.557
8.547
8.542
8.231
7.749
7.744
7.722
7.717
7.366
7.358
7.343
7.336
7.260
7.223
7.207
7.196
7.180
7.070
7.059
7.051
7.036
7.029
3.846
3.744


OMe
N
N
N

25p


9
8
7
6
5
4
3
2
1
ppm
0.98
0.94
1.00
2.06
1.06
2.13
3.00


159.678
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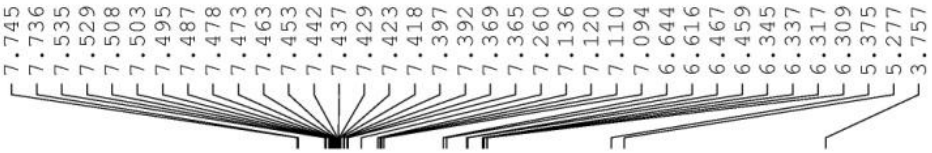
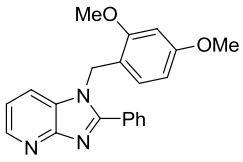
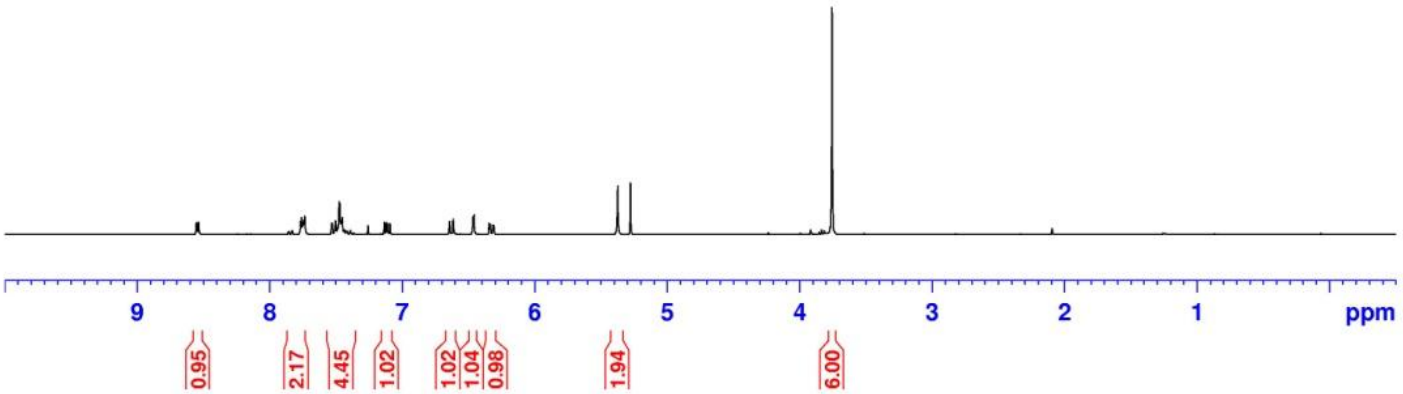
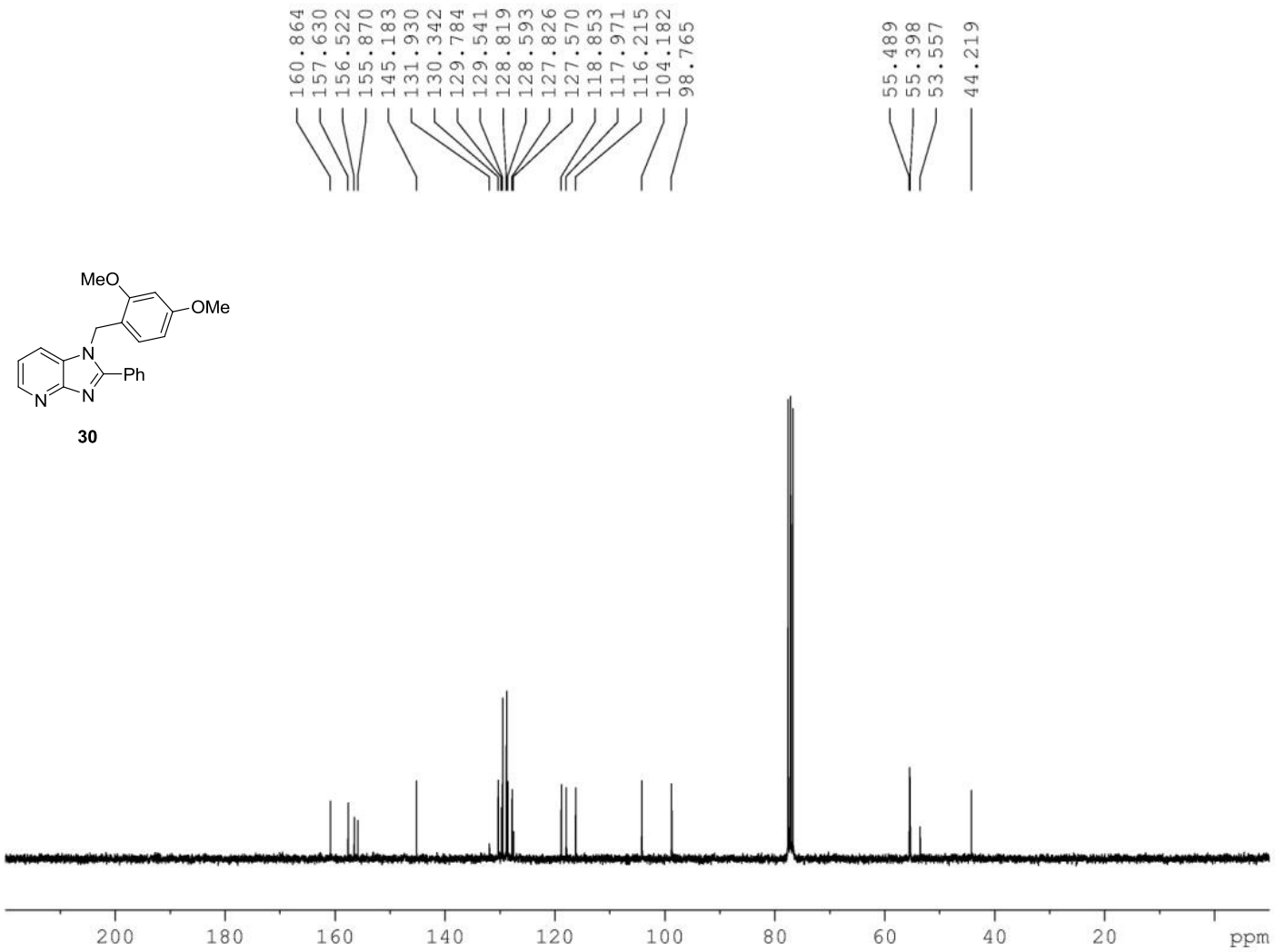
145.357
144.533
128.393
126.565
125.505
118.701
118.646
115.357
77.588
77.163
76.739
55.719
OMe
N
N
N
25p
200
180
160
140
120
100
80
60
40
20
ppm


7.745
7.736
7.535
7.529
7.508
7.503
7.495
7.487
7.478
7.473
7.463
7.453
7.442
7.437
7.429
7.423
7.418
7.397
7.392
7.369
7.365
7.260
7.136
7.120
7.110
7.094
6.644
6.616
6.467
6.459
6.345
6.337
6.317
6.309
5.375
5.277
3.757

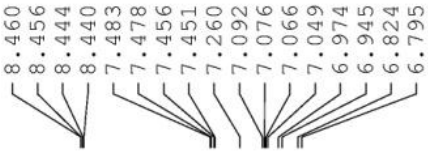

MeO
OMe
N
Ph
N
N

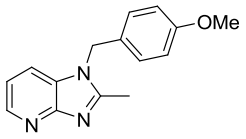
30


9
8
7
6
5
4
3
2
1
ppm
0.95
2.17
4.45
1.02
1.02
1.04
0.98
1.94
6.00

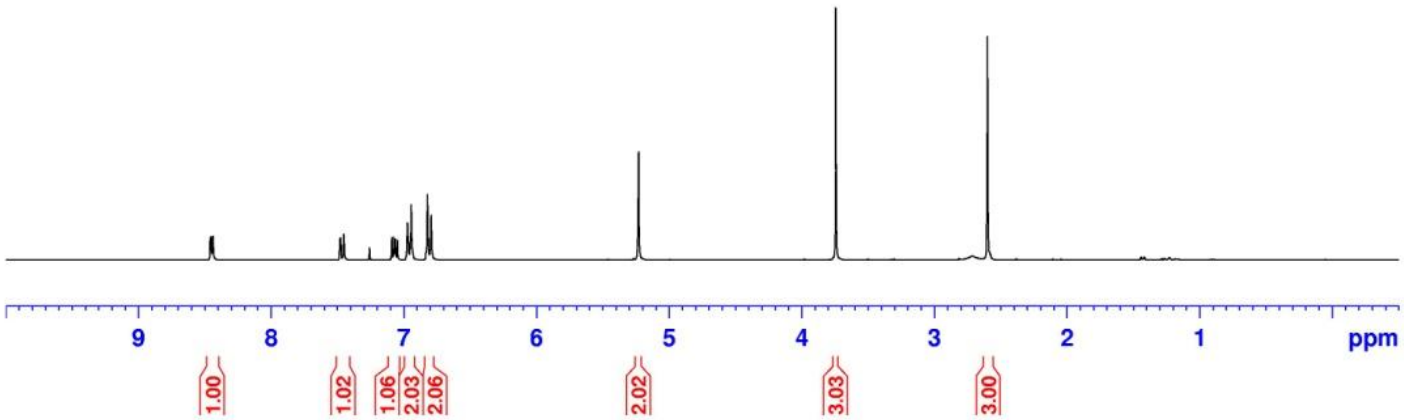

160.864
157.630
156.522
155.870
145.183
131.930
130.342
129.784
129.541
128.819
128.593
127.826
127.570
118.853
117.971
116.215
104.182
98.765
55.489
55.398
53.557
44.219
MeO
OMe
N
Ph
N
N
200
180
160
140
120
100
80
60
40
20
ppm

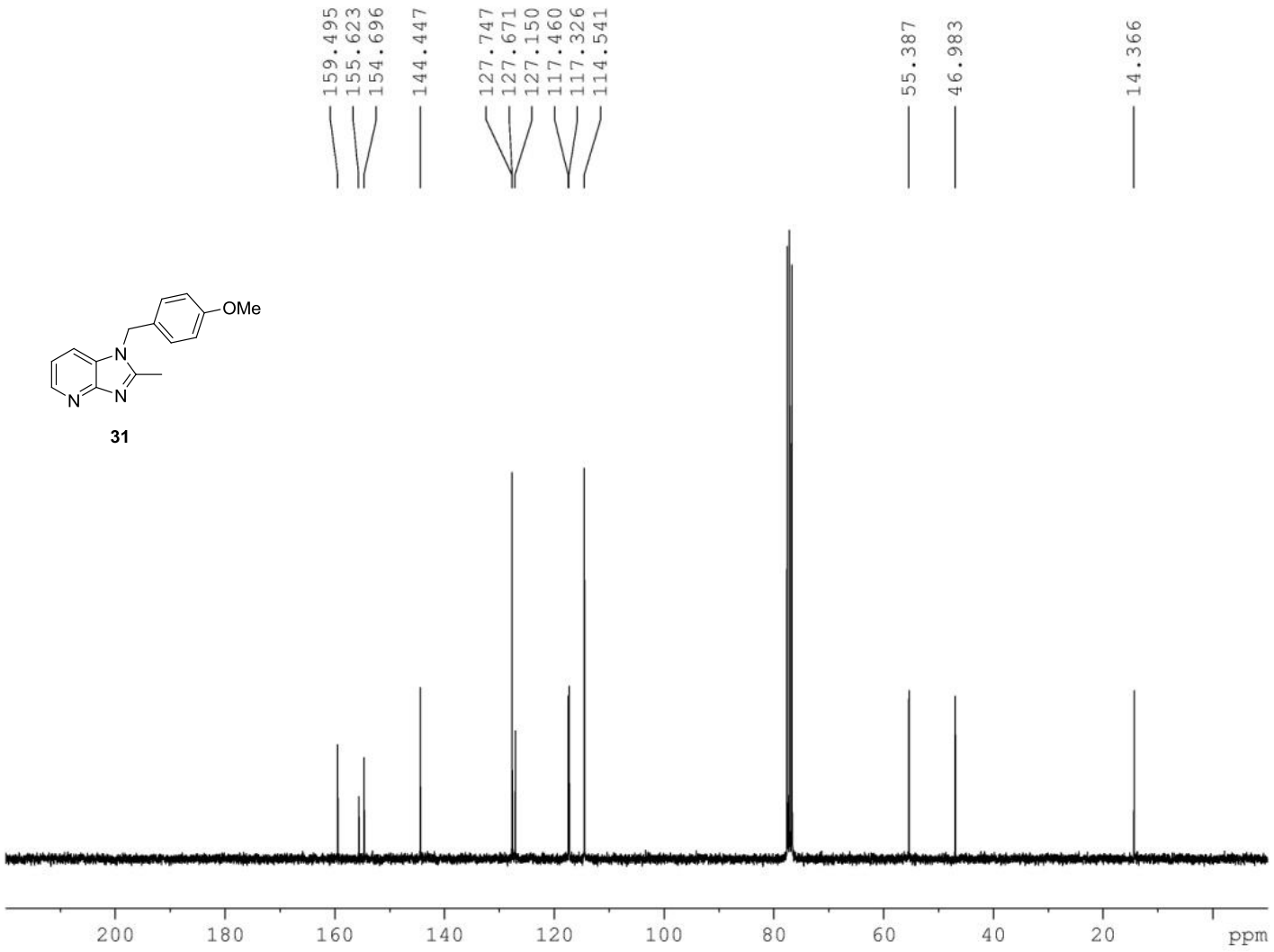
30


8.460
8.456
8.444
8.440
7.483
7.478
7.456
7.451
7.260
7.092
7.076
7.066
7.049
6.974
6.945
6.824
6.795
5.232
3.744
2.601

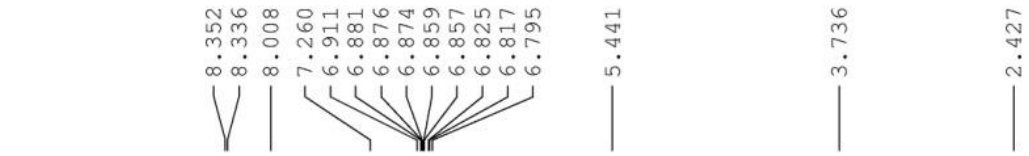

OMe
N
N
N

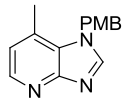
31


9
8
7
6
5
4
3
2
1
ppm
1.00
1.02
1.06
2.03
2.06
2.02
3.03
3.00

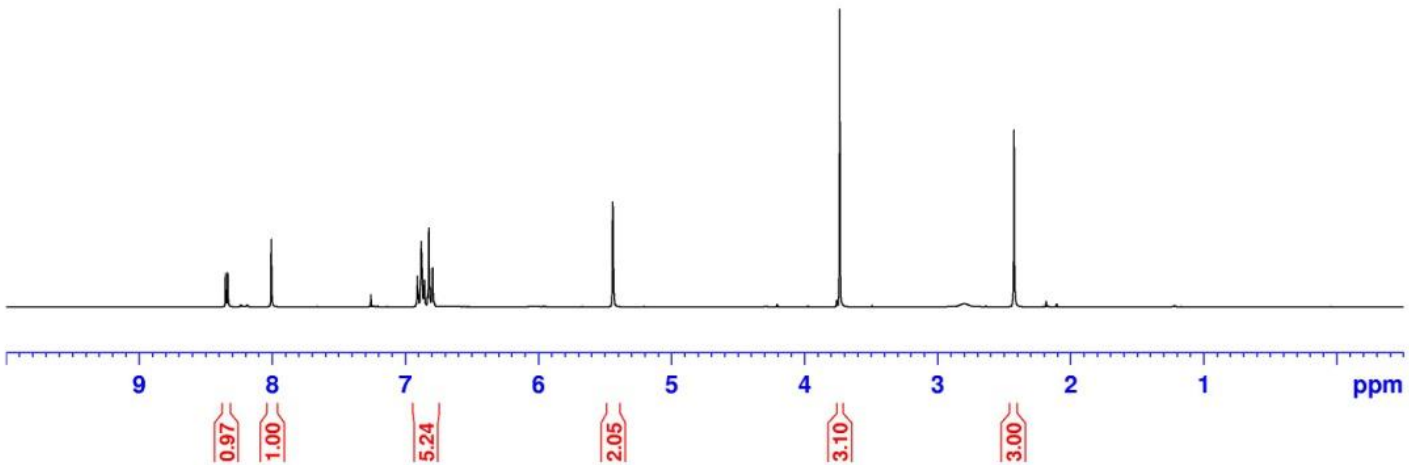

159.495
155.623
154.696
144.447
127.747
127.671
127.150
117.460
117.326
114.541
55.387
46.983
14.366
OMe
N
N
N
200
180
160
140
120
100
80
60
40
20
ppm

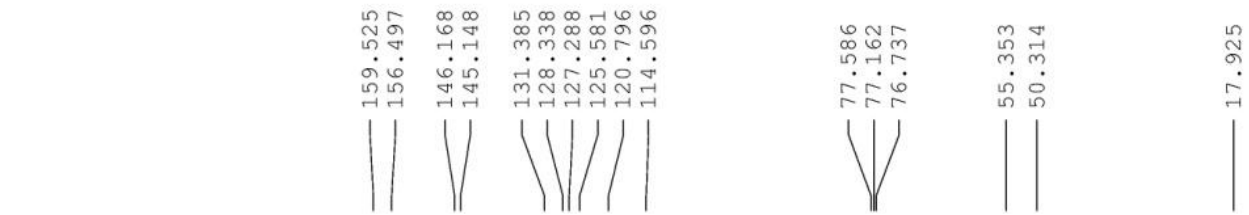
31

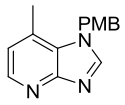

8.352
8.336
8.008
7.260
6.911
6.881
6.876
6.874
6.859
6.857
6.825
6.817
6.795
5.441
3.736
2.427


PMB
N
N
N

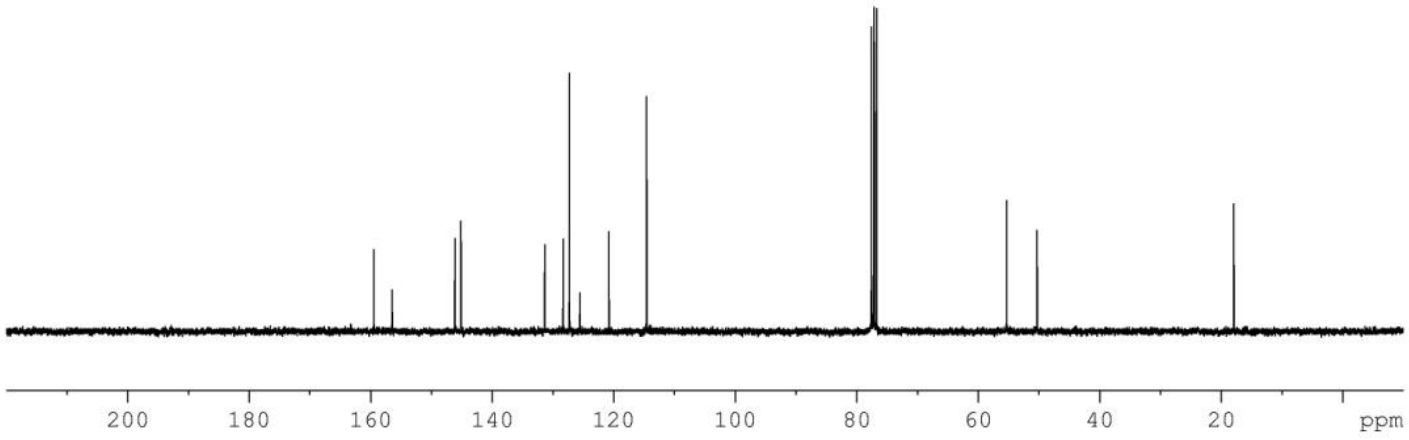
32

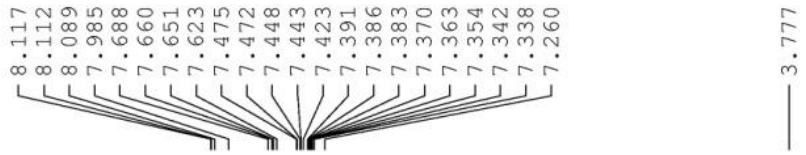

9
8
7
6
5
4
3
2
1
ppm
0.97
1.00
5.24
2.05
3.10
3.00

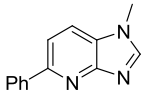

159.525
156.497
146.168
145.148
131.385
128.338
127.288
125.581
120.796
114.596
77.586
77.162
76.737
55.353
50.314
17.925


PMB
N
N
N

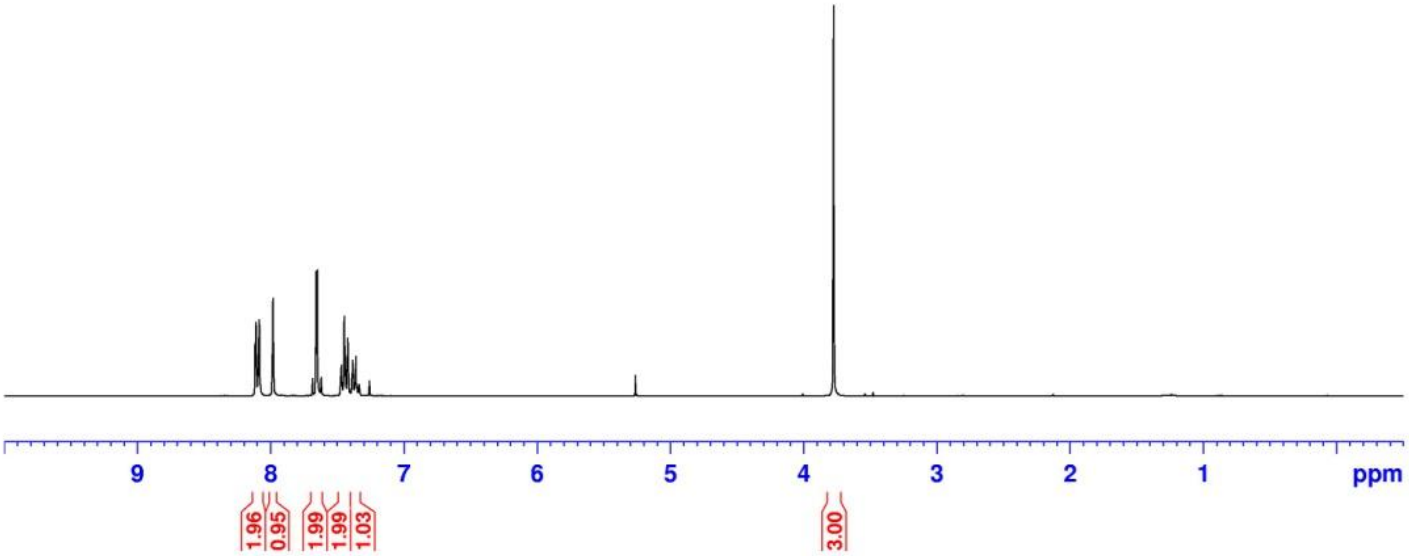
32

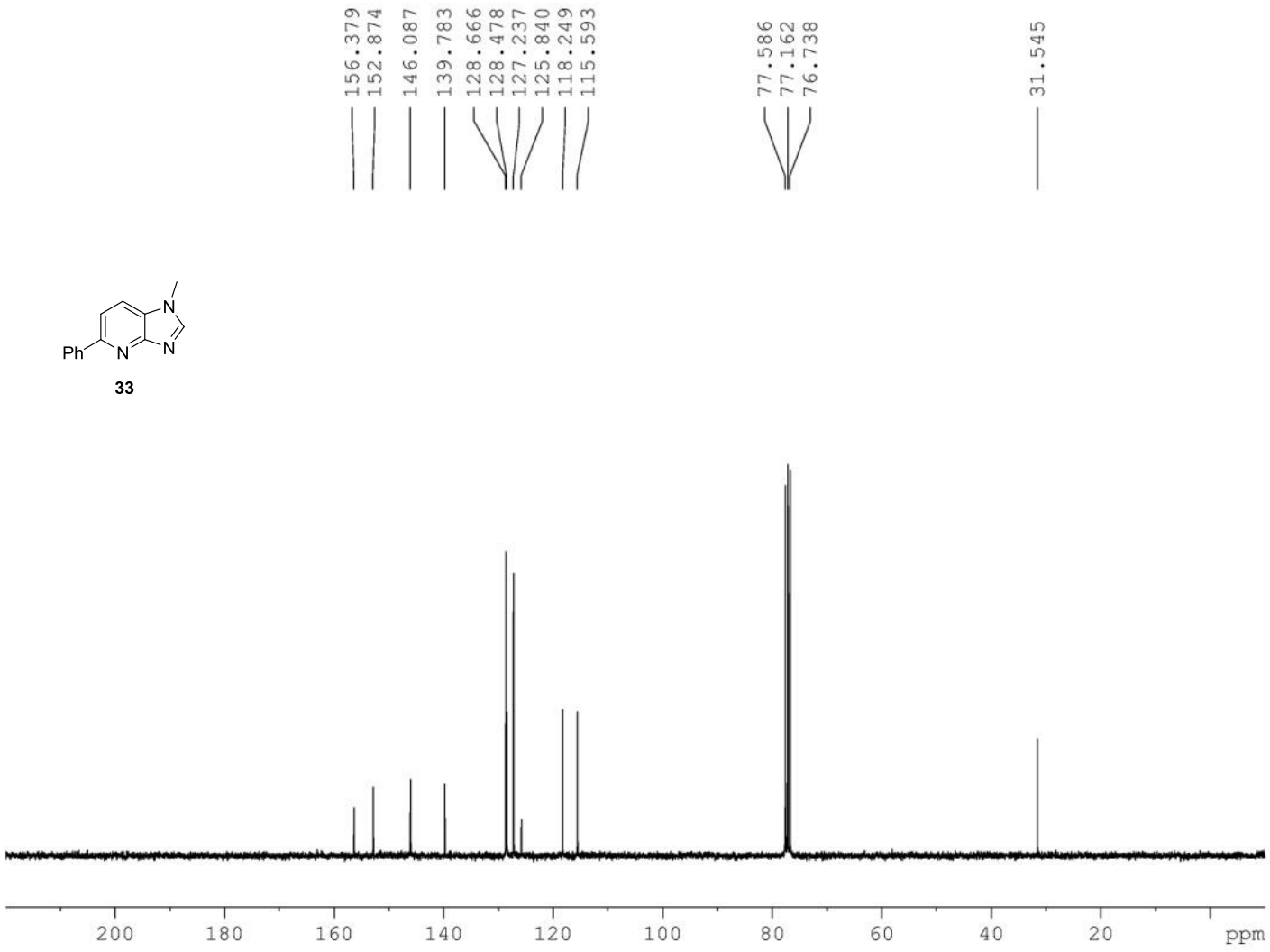

200
180
160
140
120
100
80
60
40
20
ppm


8.117
8.112
8.089
7.985
7.688
7.660
7.651
7.623
7.475
7.472
7.448
7.443
7.423
7.391
7.386
7.383
7.370
7.363
7.354
7.342
7.338
7.260
3.777

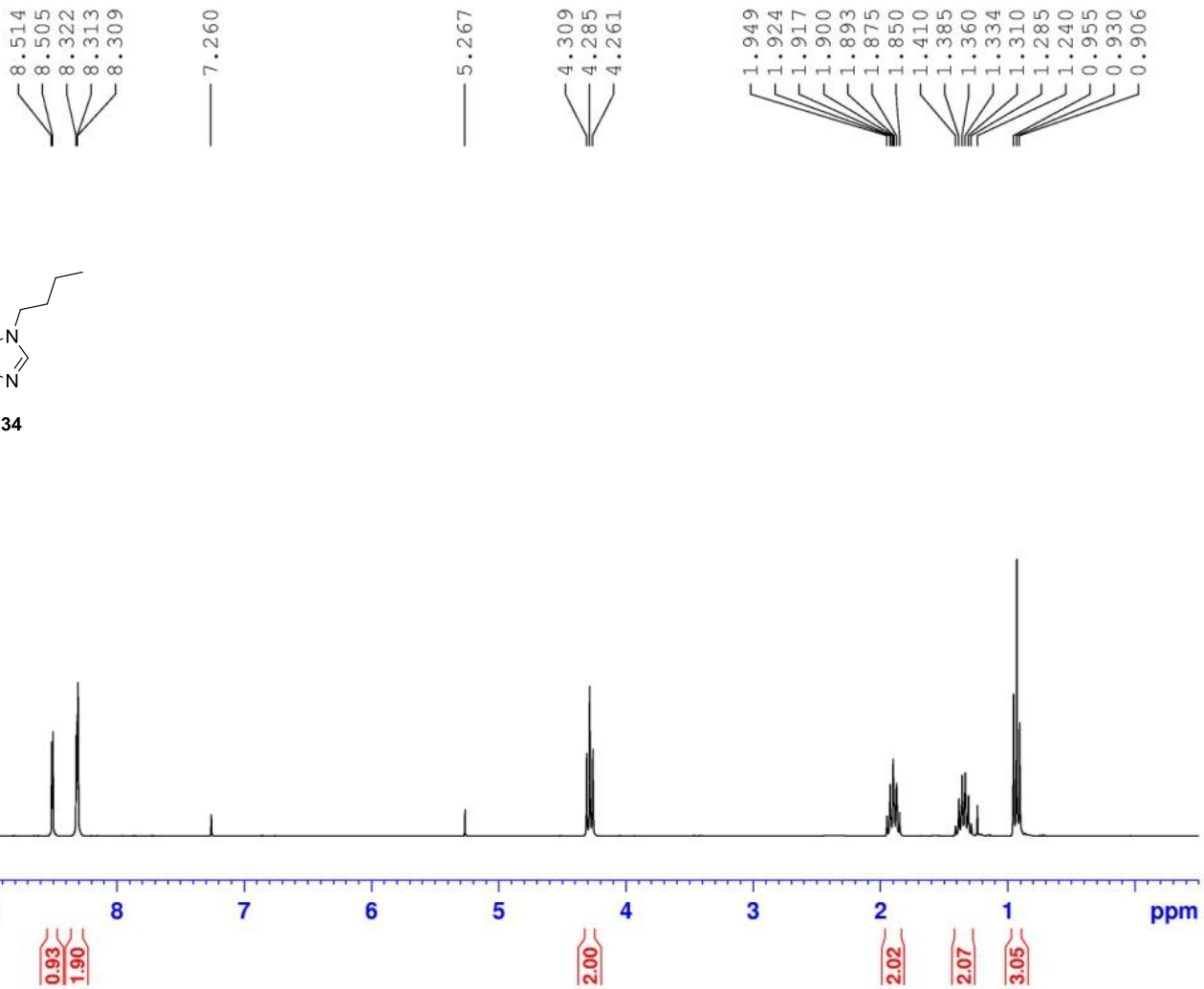

Ph
N
N
N

33

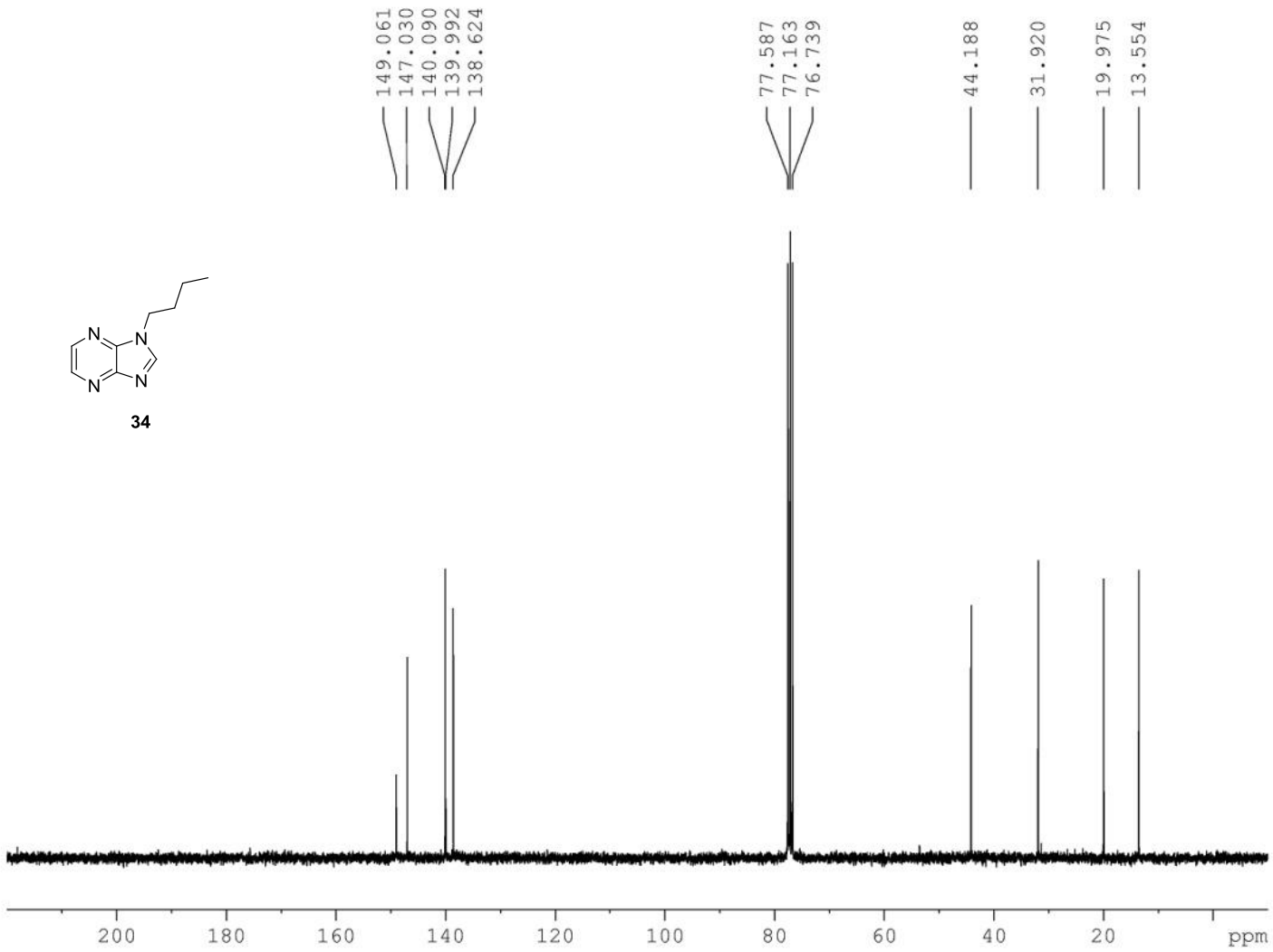

9
8
7
6
5
4
3
2
1
ppm
1.96
0.95
1.99
1.99
1.03
3.00


156.379
152.874
146.087
139.783
128.666
128.478
127.237
125.840
118.249
115.593
77.586
77.162
76.738
31.545
Ph
N
N
N
200
180
160
140
120
100
80
60
40
20
ppm

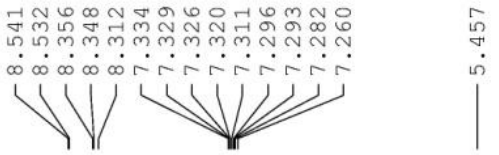
33

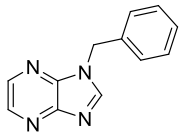

8.514
8.505
8.322
8.313
8.309
7.260
5.267
4.309
4.285
4.261
1.949
1.924
1.917
1.900
1.893
1.875
1.850
1.410
1.385
1.360
1.334
1.310
1.285
1.240
0.955
0.930
0.906
9
8
7
6
5
4
3
2
1
ppm
0.93
1.90
2.00
2.02
2.07
3.05

34

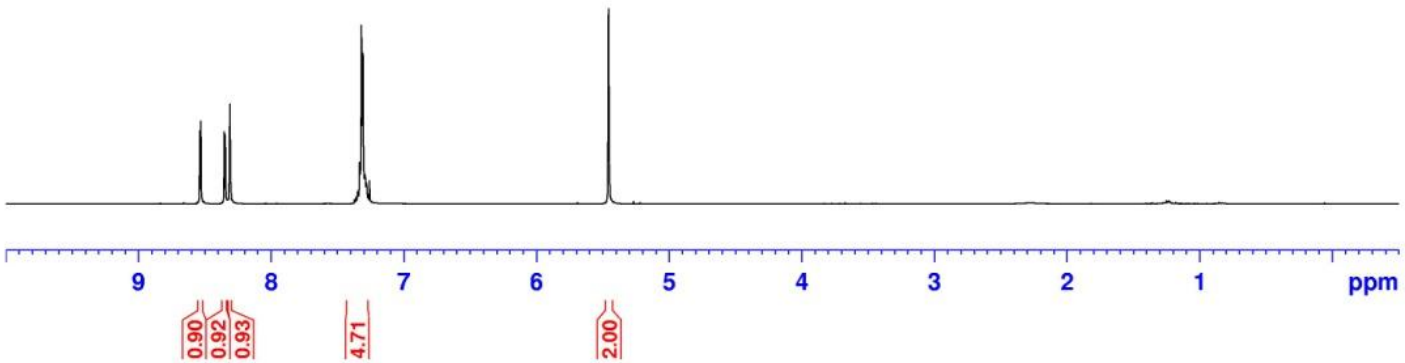

149.061
147.030
140.090
139.992
138.624
77.587
77.163
76.739
44.188
31.920
19.975
13.554
200
180
160
140
120
100
80
60
40
20
ppm

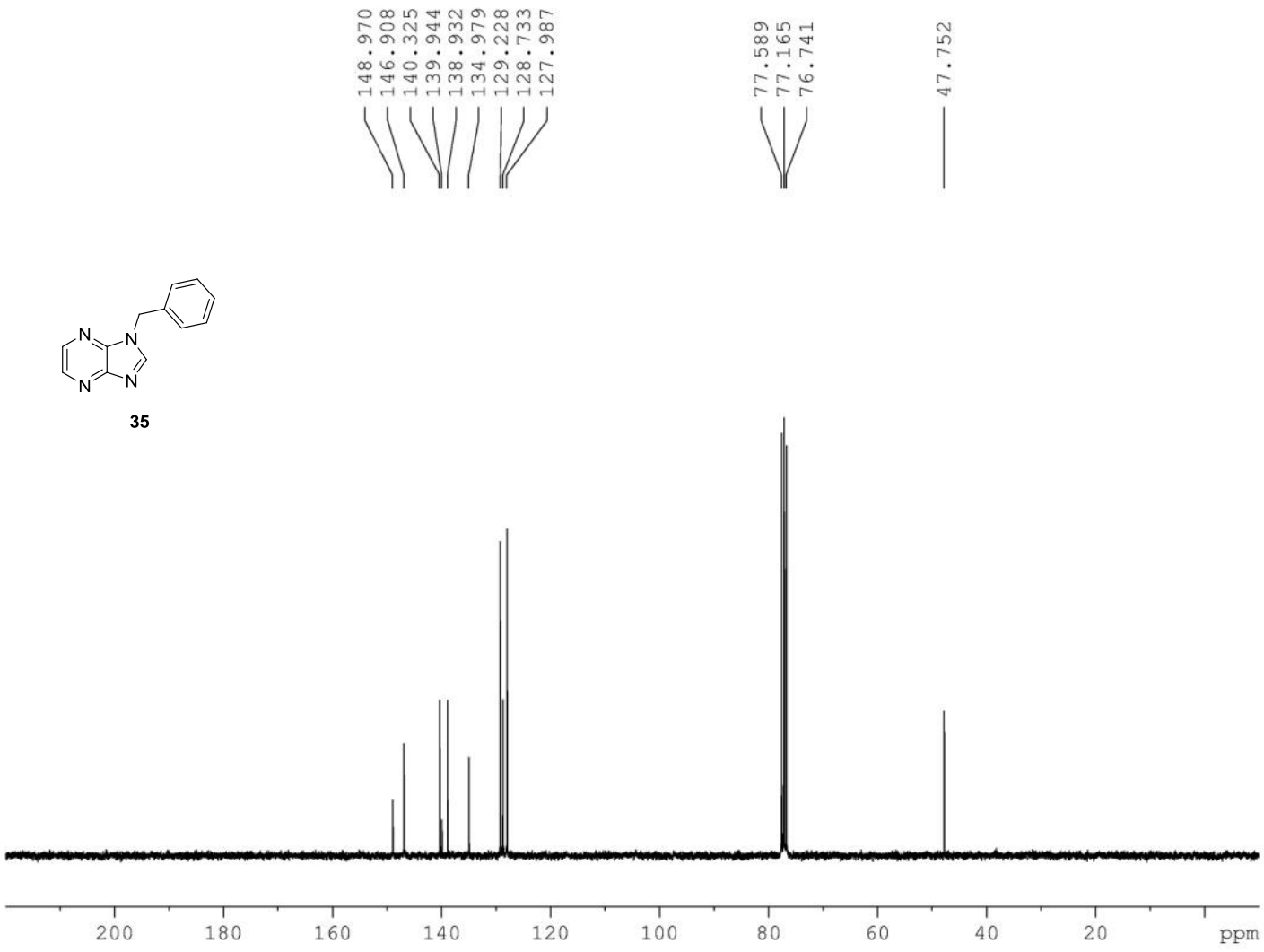
34


8.541
8.532
8.356
8.348
8.312
7.334
7.329
7.326
7.320
7.311
7.296
7.293
7.282
7.260
5.457

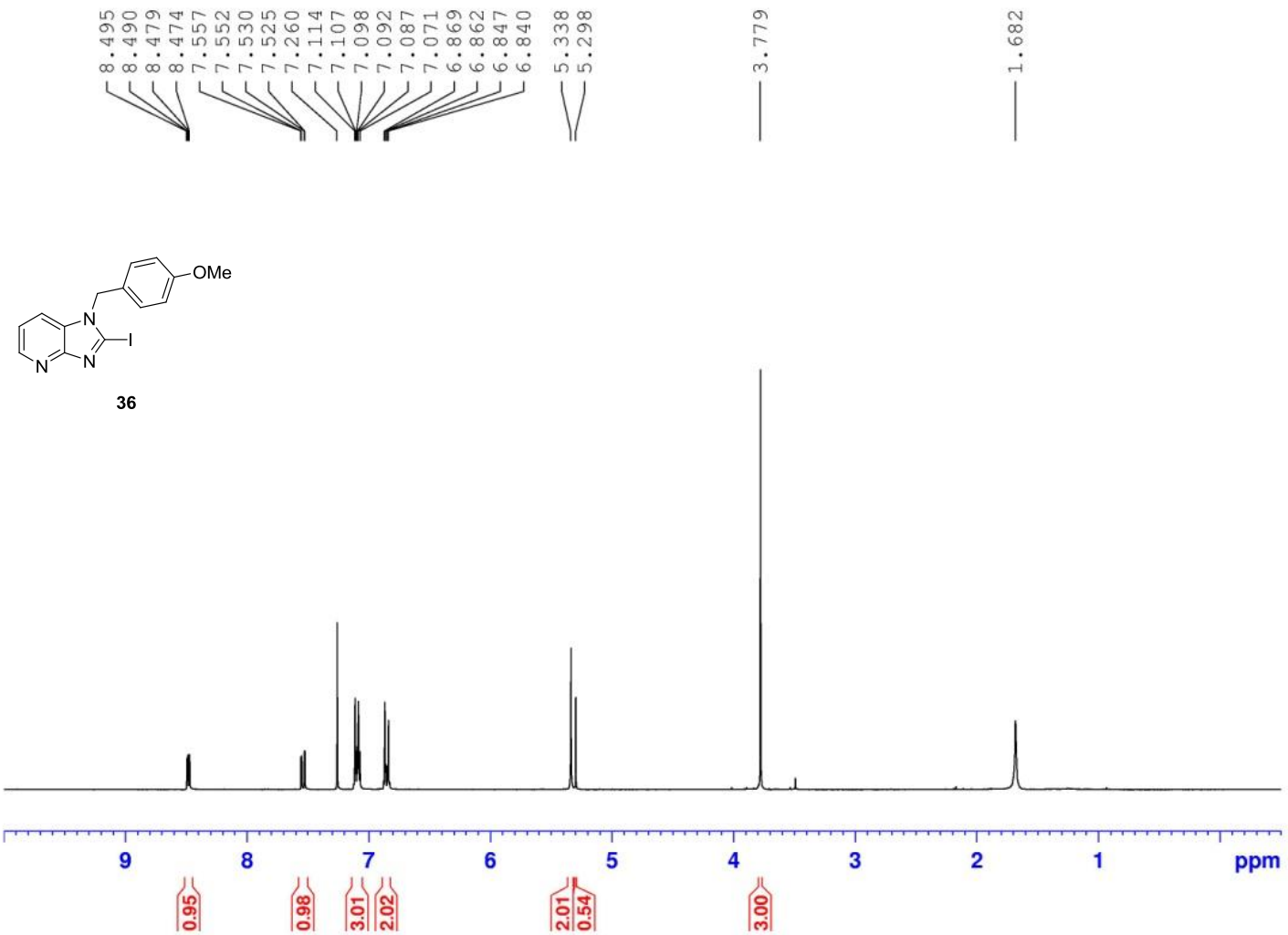


35

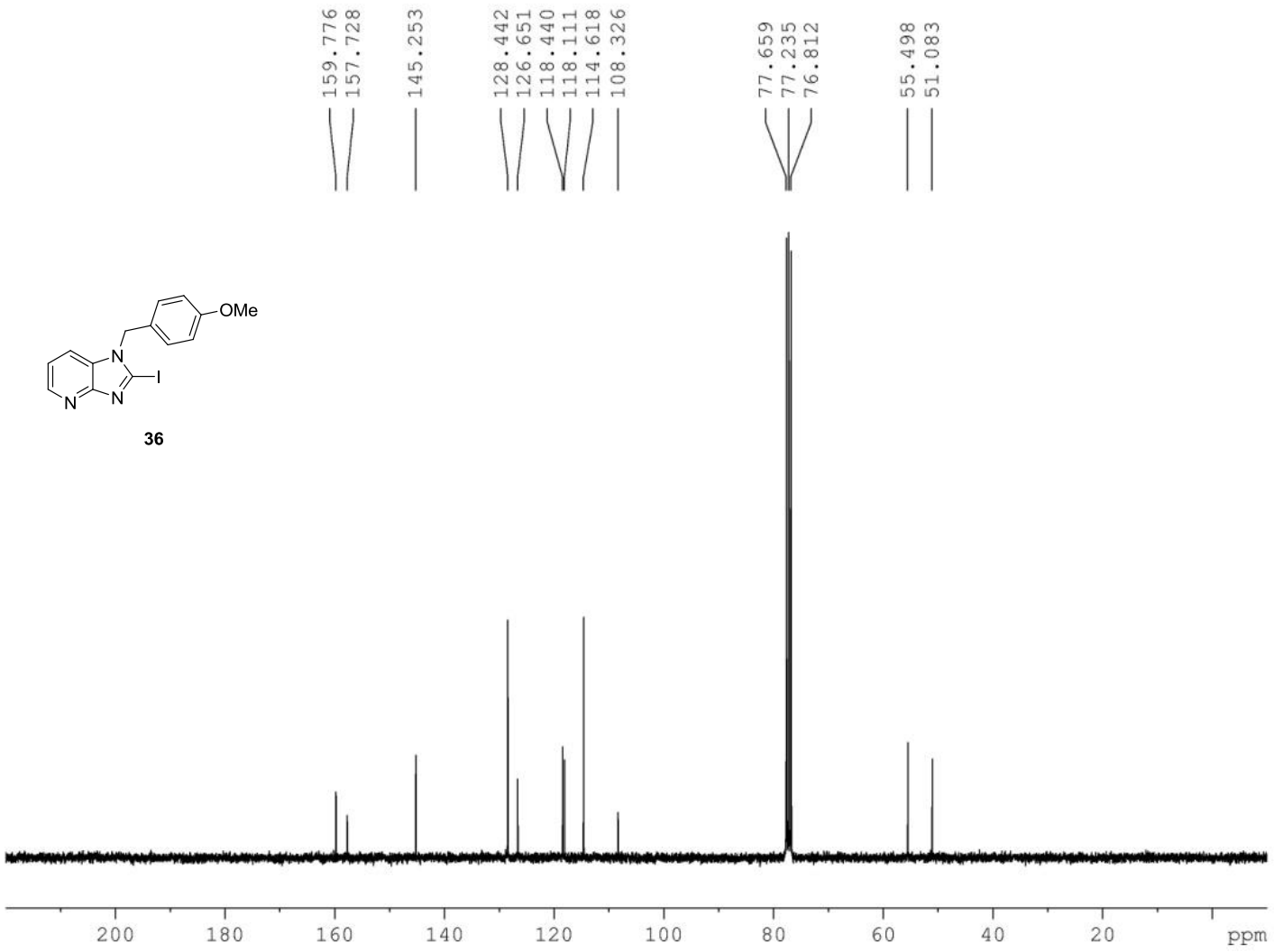

9
8
7
6
5
4
3
2
1
ppm
0.90
0.92
0.93
4.71
2.00


148.970
146.908
140.325
139.944
138.932
134.979
129.228
128.733
127.987
77.589
77.165
76.741
47.752
N
N
N
N
200
180
160
140
120
100
80
60
40
20
ppm

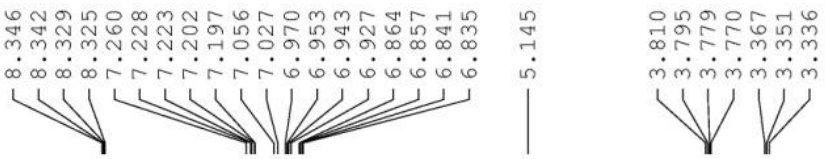
35

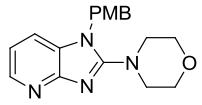

8.495
8.490
8.479
8.474
7.557
7.552
7.530
7.525
7.260
7.114
7.107
7.098
7.092
7.087
7.071
6.869
6.862
6.847
6.840
5.338
5.298
3.779
1.682
OMe
N
I
N
N
9
8
7
6
5
4
3
2
1
ppm
0.95
0.98
3.01
2.02
2.01
0.54
3.00

36

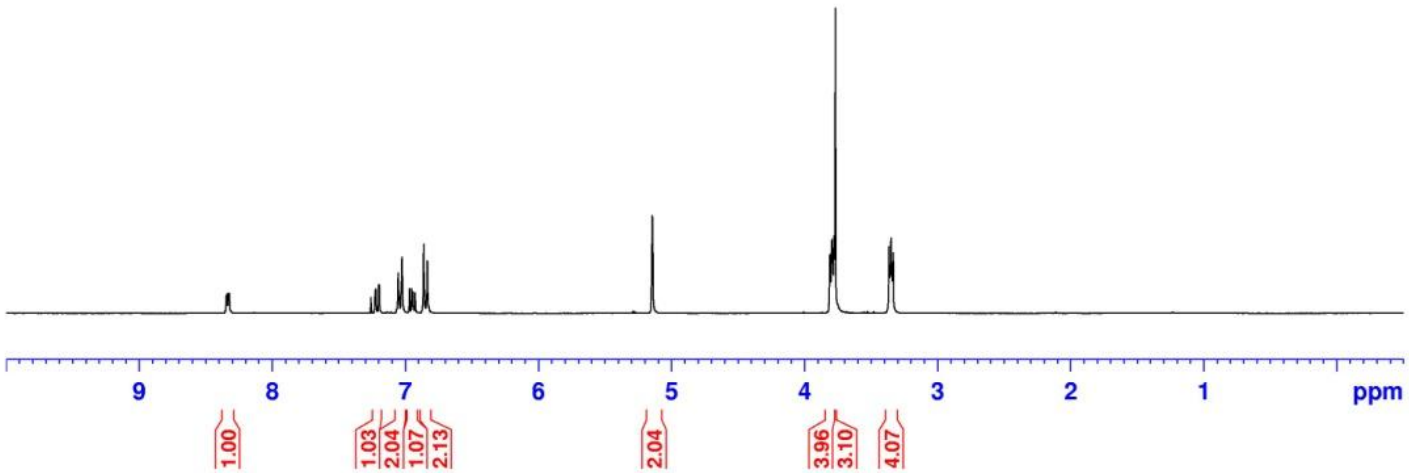

159.776
157.728
145.253
128.442
126.651
118.440
118.111
114.618
108.326
77.659
77.235
76.812
55.498
51.083
OMe
N
I
N
N
200
180
160
140
120
100
80
60
40
20
ppm

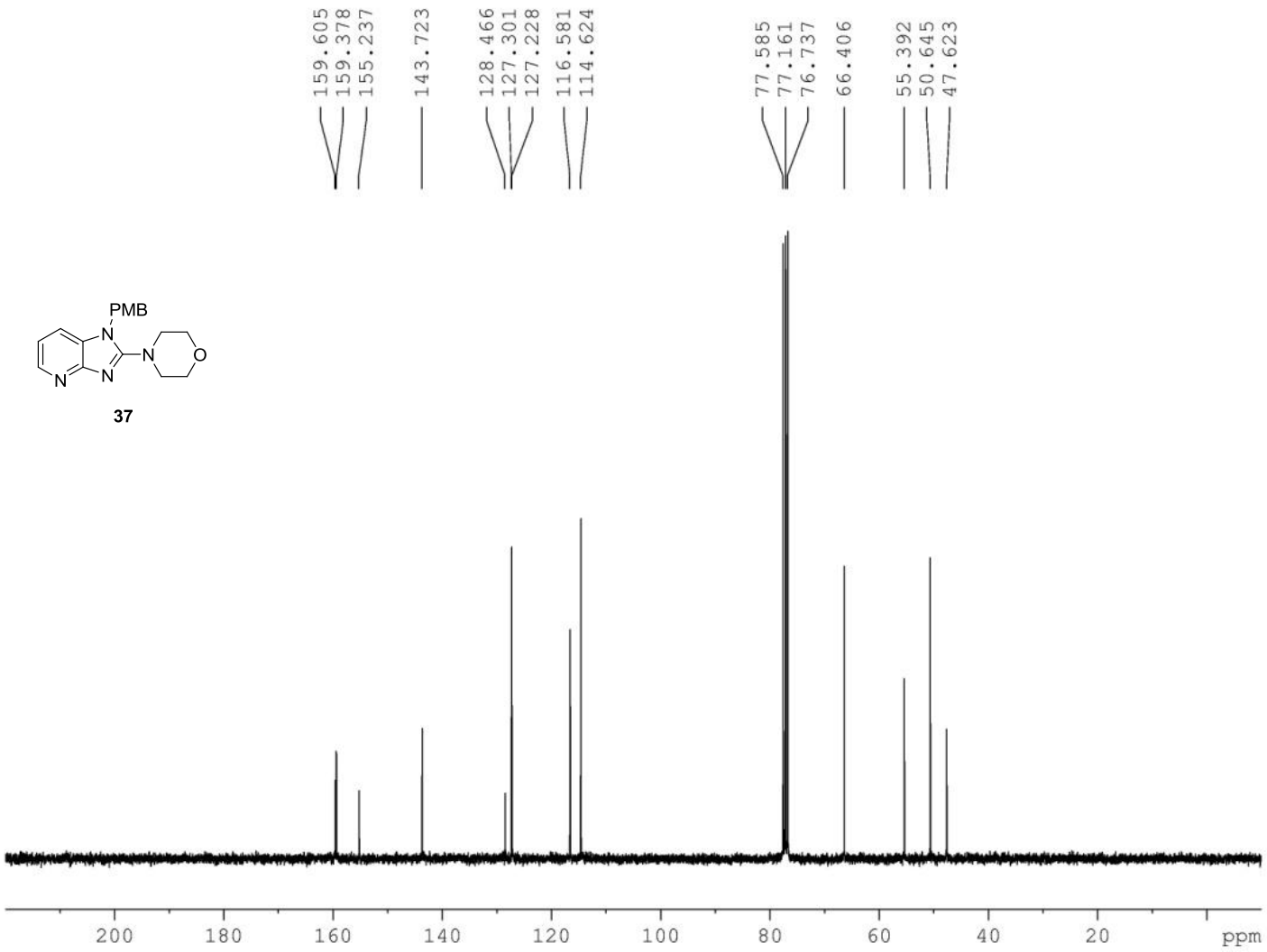
36


8.346
8.342
8.329
8.325
7.260
7.228
7.223
7.202
7.197
7.056
7.027
6.970
6.953
6.943
6.927
6.864
6.857
6.841
6.835
5.145
3.810
3.795
3.779
3.770
3.367
3.351
3.336


PMB
N
N
N
N
O

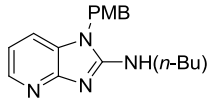
37


9
8
7
6
5
4
3
2
1
ppm
1.00
1.03
2.04
1.07
2.13
2.04
3.96
3.10
4.07

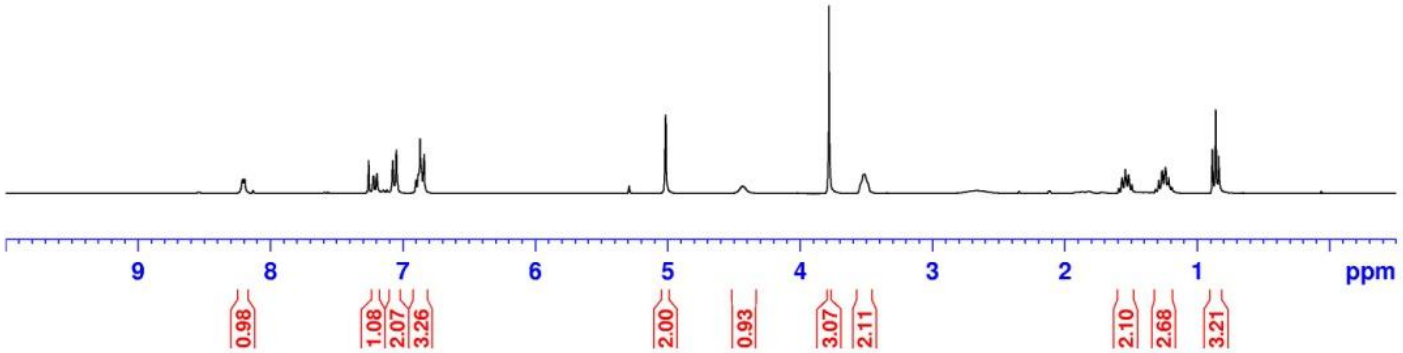

159.605
159.378
155.237
143.723
128.466
127.301
127.228
116.581
114.624
77.585
77.161
76.737
66.406
55.392
50.645
47.623
PMB
N
N
N
O
200
180
160
140
120
100
80
60
40
20
ppm

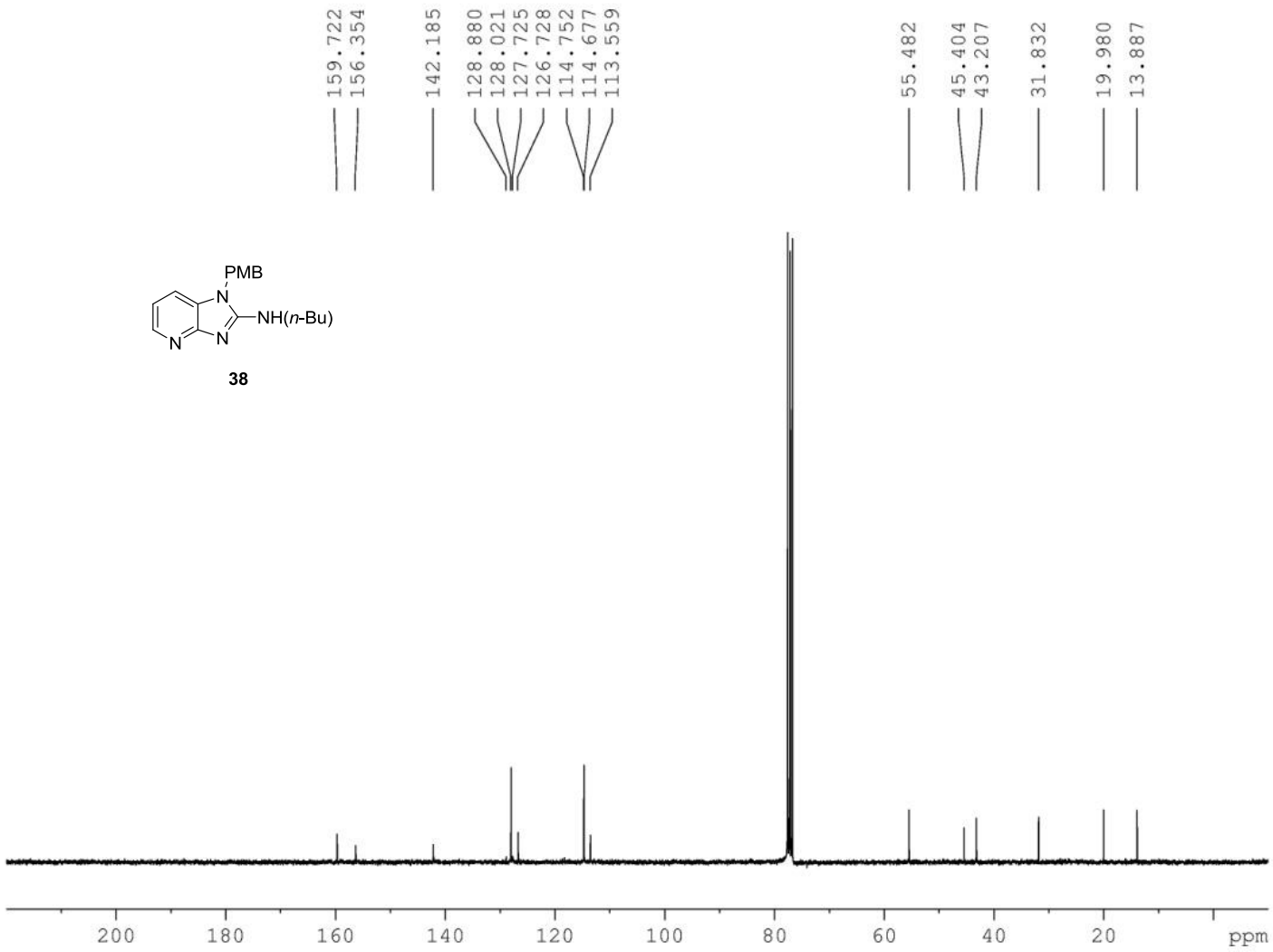
37

8.214
8.199
7.260
7.225
7.223
7.200
7.197
7.079
7.050
6.902
6.885
6.871
6.842
5.293
5.017
4.435
3.782
3.523
3.512
1.593
1.569
1.544
1.520
1.495
1.316
1.291
1.266
1.241
1.216
1.193
0.886
0.862
0.837



38

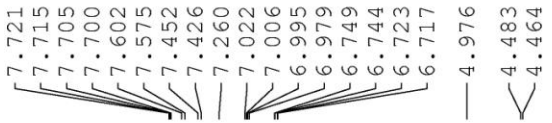


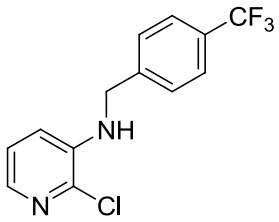

159.722
156.354
142.185
128.880
128.021
127.725
126.728
114.752
114.677
113.559
55.482
45.404
43.207
31.832
19.980
13.887
PMB
N
NH(n-Bu)
N
N
200
180
160
140
120
100
80
60
40
20
ppm

38

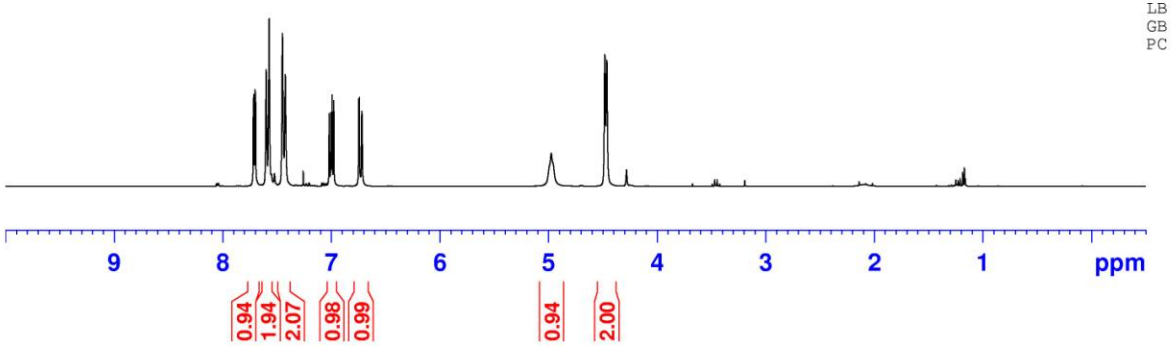
9.2 2ND GENERATION IMP

AJR-6-006
Post Column





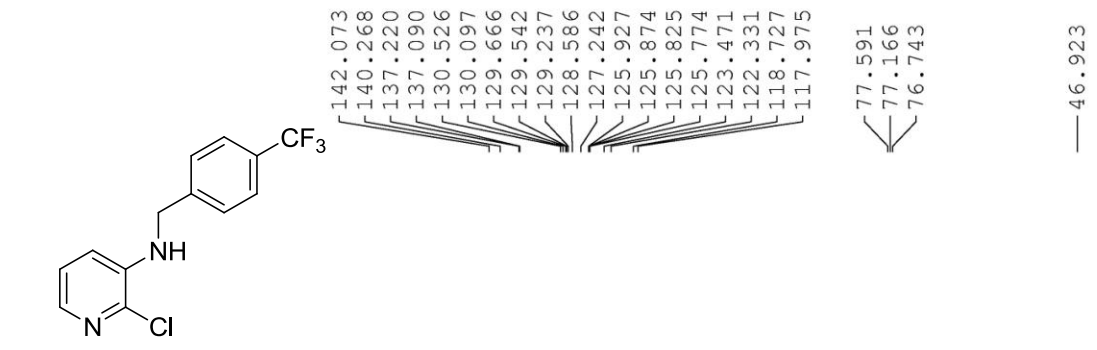
24t



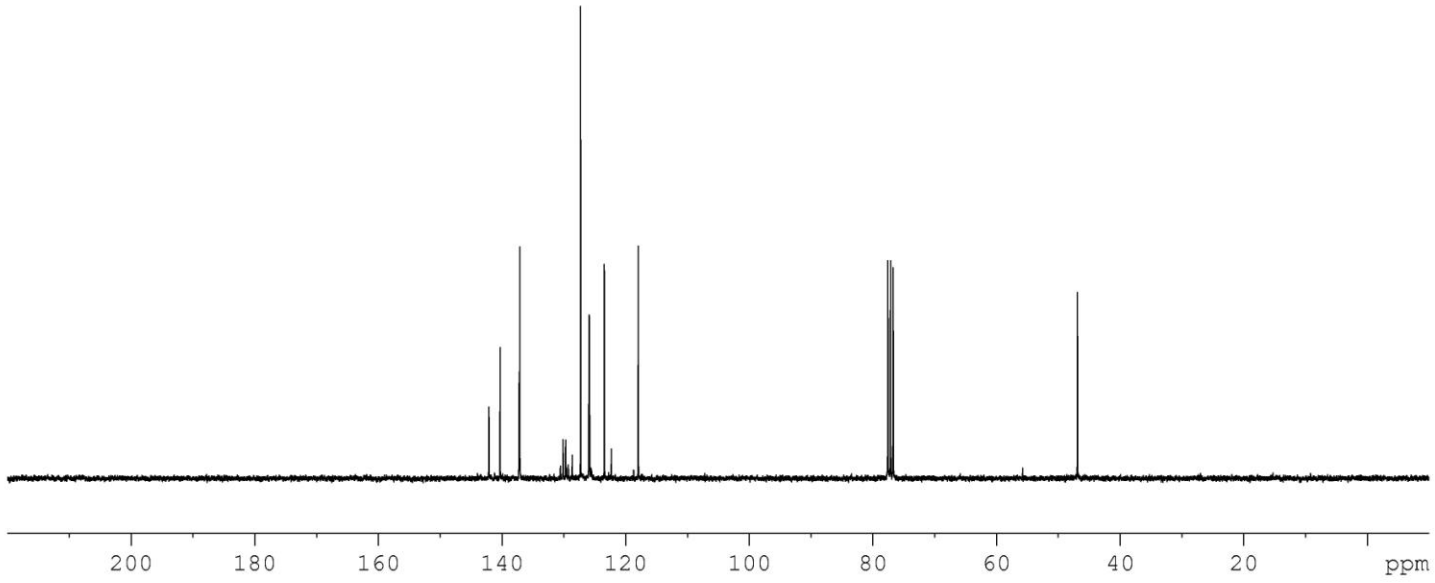
BRUKER

NAME	AJR-6-006
EXPNO	7
PROCNO	1
Date_	20130801
Time	18.44
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	57
DW	139.200 usec
DE	54.00 usec
TE	296.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300061 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

AJR-6-006

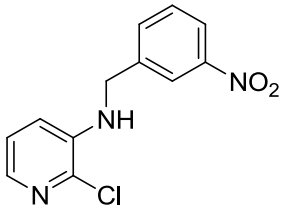

142.073
140.268
137.220
137.090
130.526
130.097
129.666
129.542
129.237
128.586
127.242
125.927
125.874
125.825
125.774
123.471
122.331
118.727
117.975
77.591
77.166
76.743
46.923
CF3
NH
N
Cl

24t


200
180
160
140
120
100
80
60
40
20
ppm

TW-1-40
after recrystalization

8.151 8.148 7.785 7.779 7.769 7.764 7.707 7.705 7.681 7.679 7.580 7.553 7.527 7.260 7.065 7.049 7.038 7.022 6.767 6.762 6.740 6.735 4.997 4.991 4.974 4.548

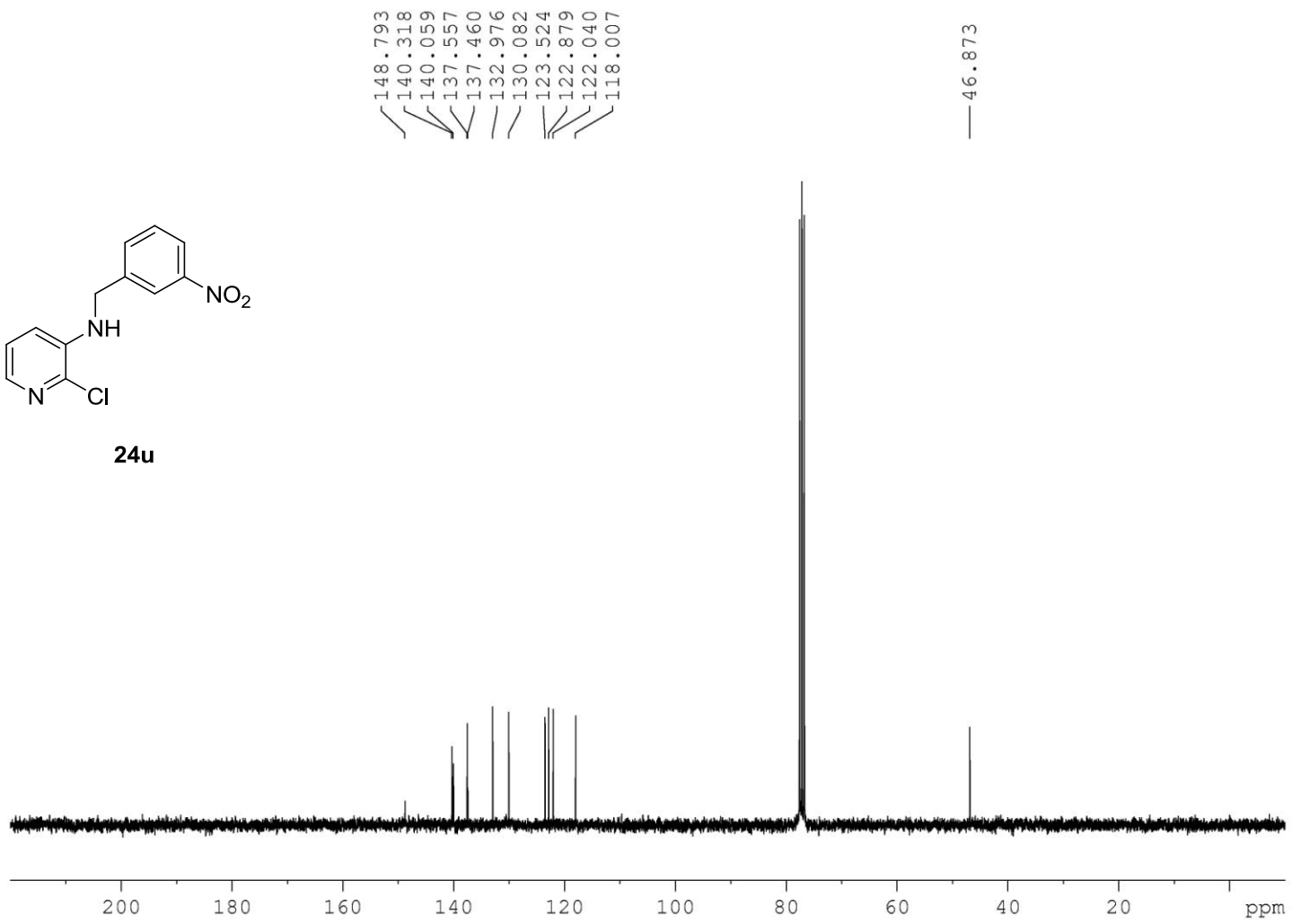


24u

BRUKER

NAME	Tw-1-40	
EXPNO	1	
PROCNO	1	
Date_	20120618	
Time	14.45	
INSTRUM	spect	
PROBHD	5 mm QNP 1H/1	
PULPROG	zg	
TD	32768	
SOLVENT	CDCl3	
NS	16	
DS	0	
SWH	3591.954	Hz
FIDRES	0.109618	Hz
AQ	4.5613556	sec
RG	812.7	
DW	139.200	usec
DE	54.00	usec
TE	296.2	K
D1	3.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	9.75	usec
PL1	0.00	dB
SFO1	300.1315007	MHz
SI	32768	
SF	300.1300062	MHz
WDW	EM	
SSB	0	
LB	0.20	Hz
GB	0	
PC	1.00	

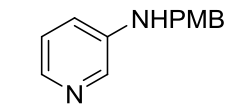
tw-1-40


148.793
140.318
140.059
137.557
137.460
132.976
130.082
123.524
122.879
122.040
118.007
46.873
NO2
NH
N
Cl
200
180
160
140
120
100
80
60
40
20
ppm

24u

AJR-5-263
Post Column

7.957 7.946 7.941 7.282 7.253 7.073 7.071 7.058 7.056 7.045 7.044 7.030 7.028 6.903 6.893 6.886 6.879 6.874 6.870 6.864 6.851 6.846 6.841 6.837 4.258 4.241 4.143 3.791



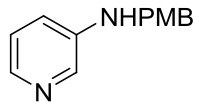
39

BRUKER

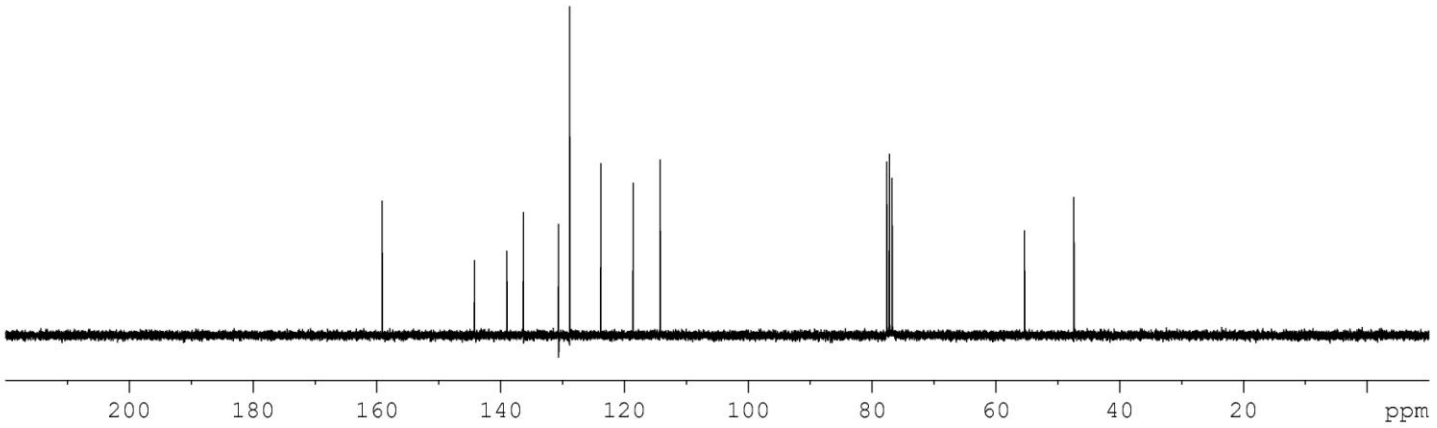
NAME	AJR-5-263	
EXPNO	2	
PROCNO	1	
Date_	20130114	
Time	16.57	
INSTRUM	spect	
PROBHD	5 mm QNP 1H/1	
PULPROG	zg	
TD	32768	
SOLVENT	CDCl3	
NS	16	
DS	0	
SWH	3591.954	Hz
FIDRES	0.109618	Hz
AQ	4.5613556	sec
RG	128	
DW	139.200	usec
DE	54.00	usec
TE	298.2	K
D1	5.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	9.75	usec
PL1	0.00	dB
SFO1	300.1315007	MHz
SI	32768	
SF	300.1300061	MHz
WDW	EM	
SSB	0	
LB	0.20	Hz
GB	0	
PC	1.00	

AJR-5-263
Post Column

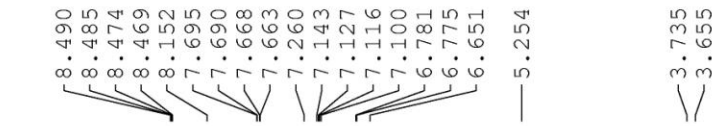
159.113
144.170
138.957
136.303
130.607
128.843
123.778
118.592
114.230
77.589
77.165
76.741
55.397
47.426

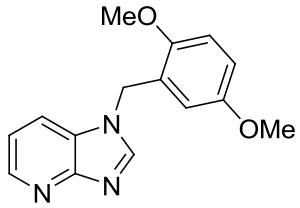


39



AJR-5-271
Post Column

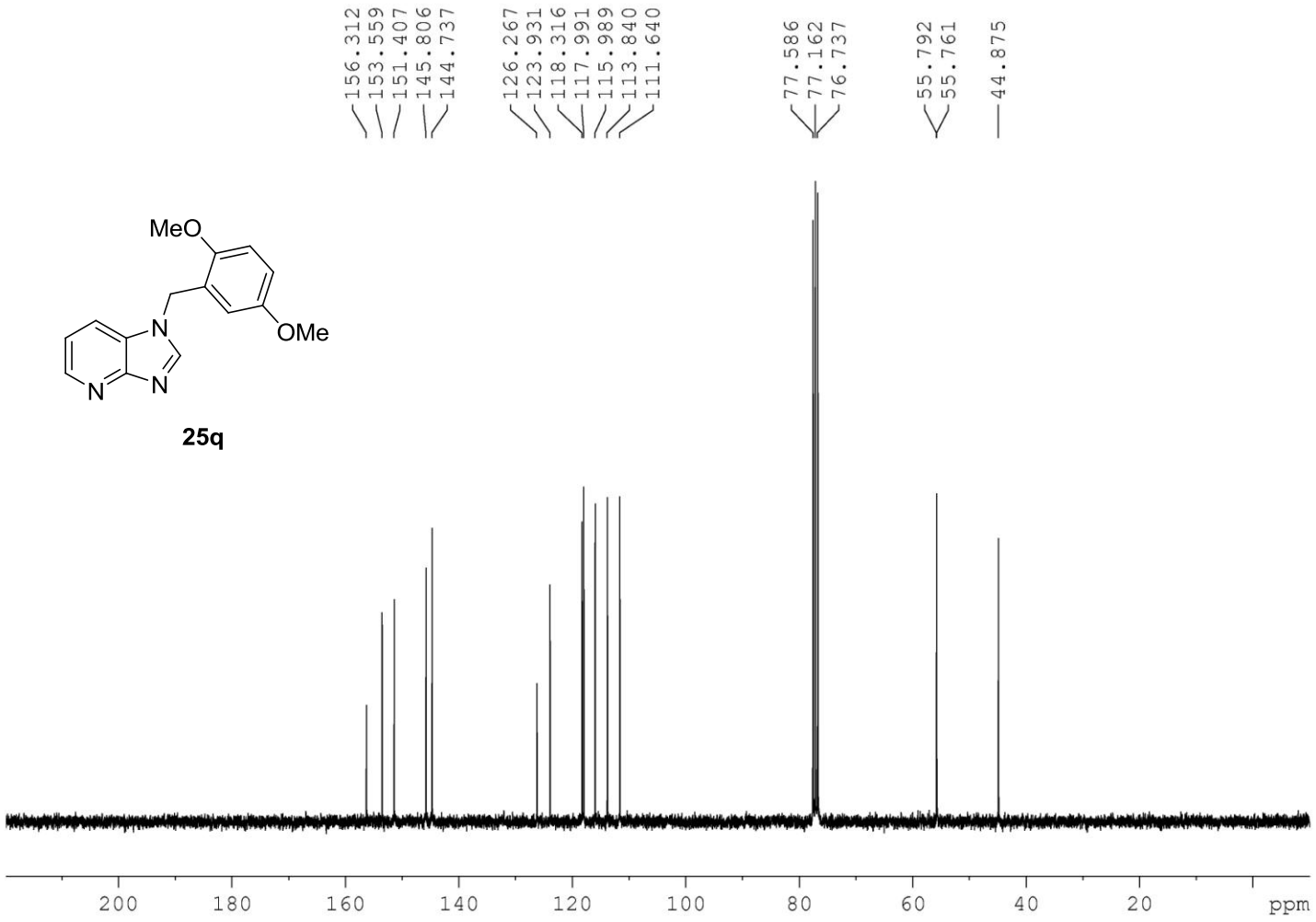




25q

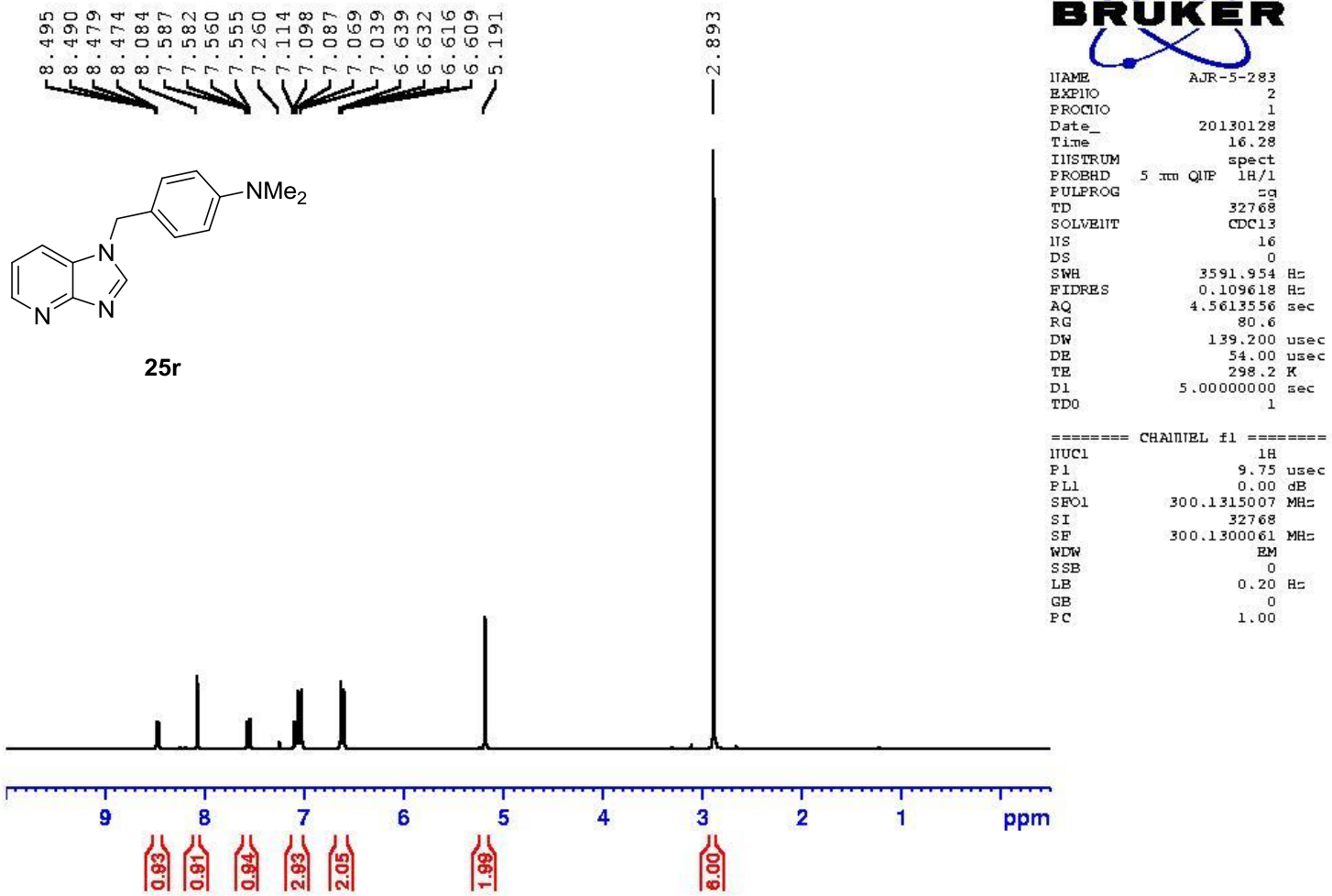
NAME	AJR-5-271	
EXPNO	2	
PROCNO	1	
Date_	20130130	
Time	16.26	
INSTRUM	spect	
PROBHD	5 mm QNP 1H/1	
PULPROG	zg	
TD	32768	
SOLVENT	CDCl3	
NS	16	
DS	0	
SWH	3591.954	Hz
FIDRES	0.109618	Hz
AQ	4.5613556	sec
RG	80.6	
DW	139.200	usec
DE	54.00	usec
TE	298.2	K
D1	5.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	9.75	usec
PL1	0.00	dB
SFO1	300.1315007	MHz
SI	32768	
SF	300.1300061	MHz
WDW	EM	
SSB	0	
LB	0.20	Hz
GB	0	
PC	1.00	

AJR-5-271
Post Column



25q

AJR-5-283
Post Column

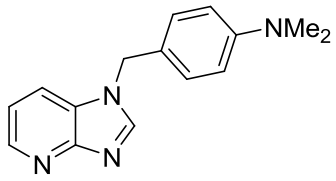


25r

NAME	AJR-5-283
EXPNO	2
PROCNO	1
Date_	20130128
Time	16.28
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	80.6
DW	139.200 usec
DE	54.00 usec
TE	298.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300061 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

AJR-5-283
Post Carbon

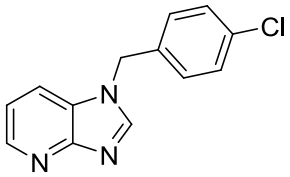
156.582
150.526
145.162
144.796
128.660
126.223
121.545
118.543
117.968
112.506
77.587
77.162
76.738
49.292
40.357



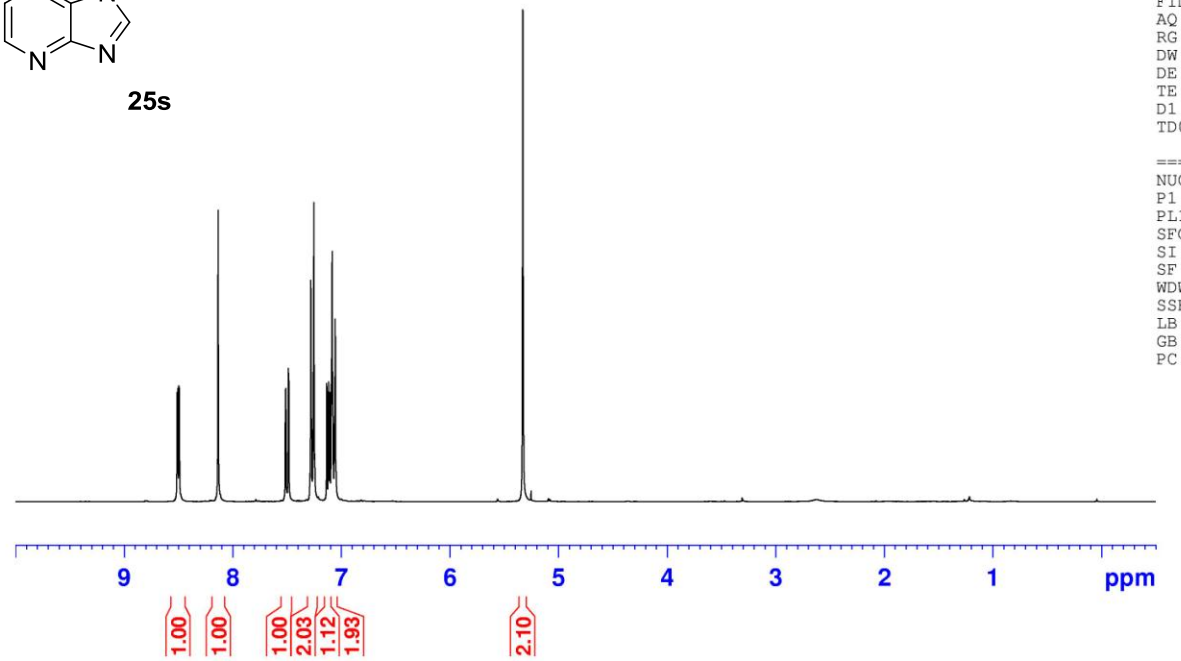
25r

AJR-5-244
Post Column

8.514
8.509
8.499
8.493
8.137
7.518
7.513
7.491
7.486
7.283
7.255
7.136
7.120
7.109
7.093
7.087
7.058
5.330



25s

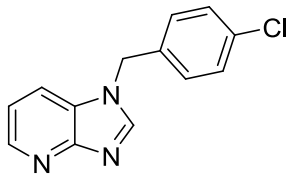


BRUKER

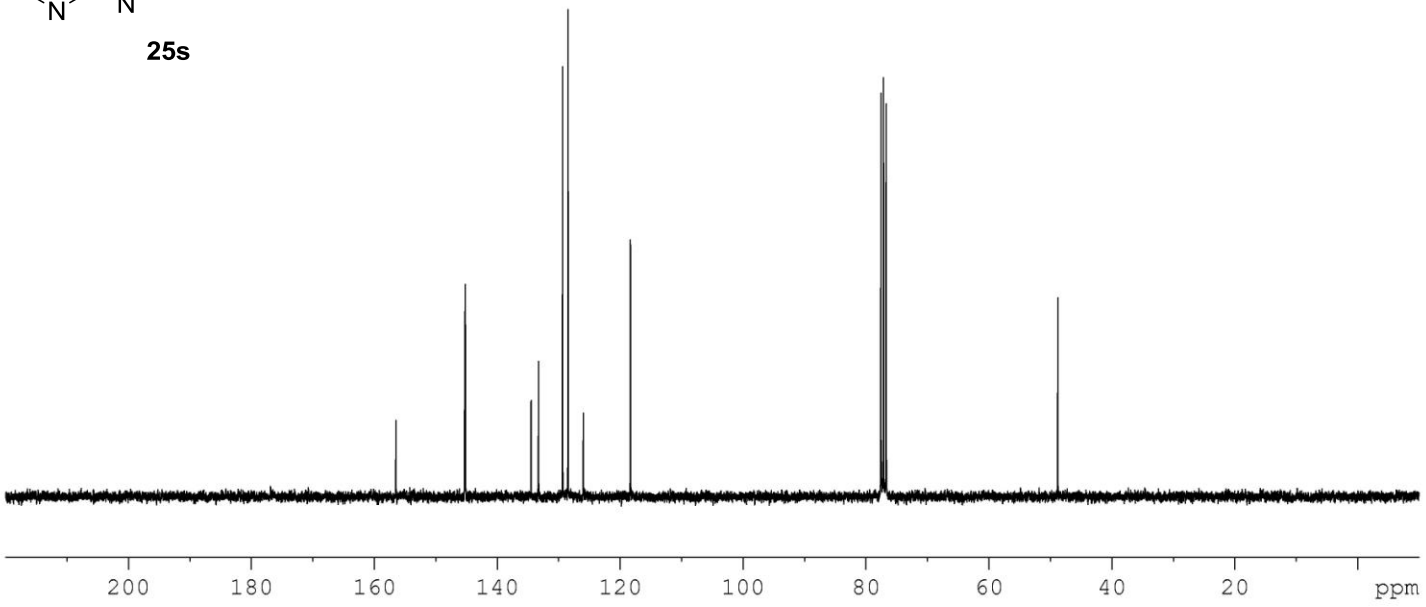
NAME	AJR-5-244	
EXPNO	2	
PROCNO	1	
Date_	20121214	
Time	15.43	
INSTRUM	spect	
PROBHD	5 mm QNP 1H/1	
PULPROG	zg	
TD	32768	
SOLVENT	CDCl3	
NS	16	
DS	0	
SWH	3591.954	Hz
FIDRES	0.109618	Hz
AQ	4.5613556	sec
RG	101.6	
DW	139.200	usec
DE	54.00	usec
TE	437.2	K
D1	5.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	9.75	usec
PL1	0.00	dB
SFO1	300.1315007	MHz
SI	32768	
SF	300.1300061	MHz
WDW	EM	
SSB	0	
LB	0.20	Hz
GB	0	
PC	1.00	

AJR-5-244
Post Column

156.509
145.300
145.201
134.519
133.295
129.388
128.514
126.019
118.354
118.336
77.589
77.164
76.740
48.812

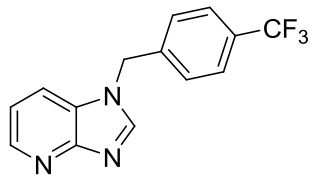


25s



AJR-6-016
Post Column & Wash

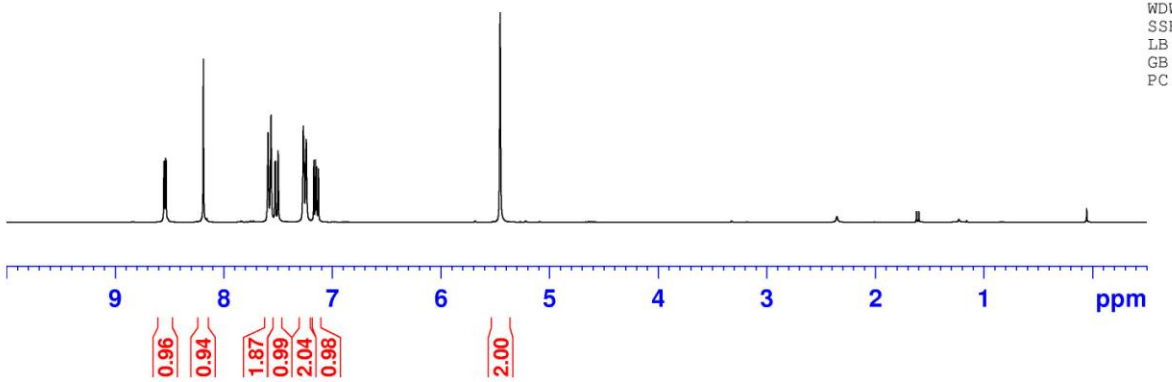
8.554
8.549
8.538
8.533
8.190
7.594
7.567
7.530
7.525
7.503
7.498
7.269
7.260
7.242
7.173
7.157
7.146
7.130
5.456



25t

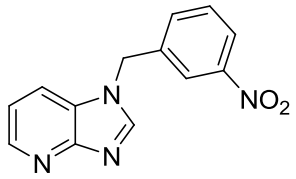
BRUKER

NAME	AJR-6-016	
EXPNO	6	
PROCNO	1	
Date_	20130311	
Time	18.04	
INSTRUM	spect	
PROBHD	5 mm QNP 1H/1	
PULPROG	zg	
TD	32768	
SOLVENT	CDCl3	
NS	16	
DS	0	
SWH	3591.954	Hz
FIDRES	0.109618	Hz
AQ	4.5613556	sec
RG	161.3	
DW	139.200	usec
DE	54.00	usec
TE	298.2	K
D1	5.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	9.75	usec
PL1	0.00	dB
SFO1	300.1315007	MHz
SI	32768	
SF	300.1300062	MHz
WDW	EM	
SSB	0	
LB	0.20	Hz
GB	0	
PC	1.00	

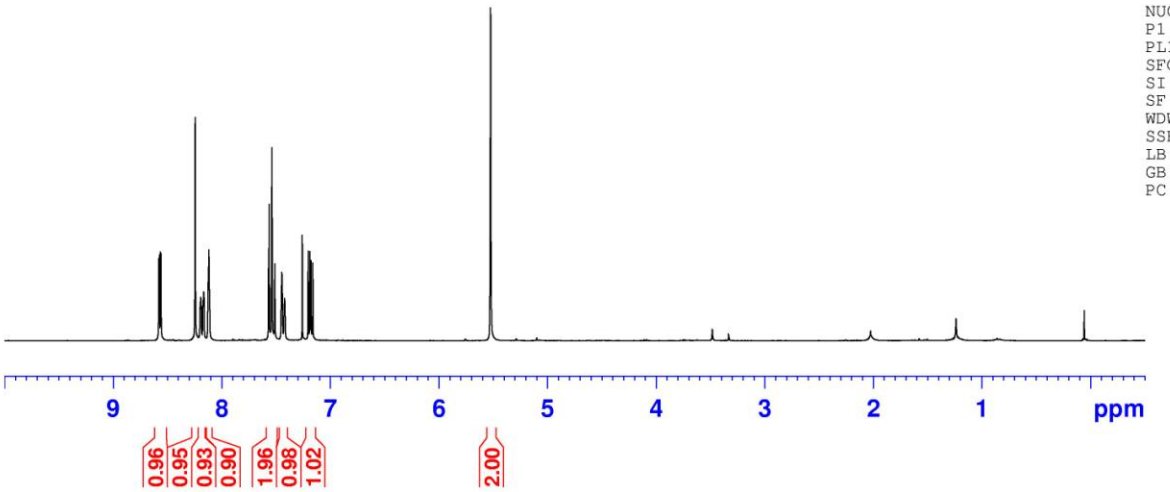


AJR-5-290
Post Column

8.176 8.172 8.168 8.165 8.127 8.121 8.116 7.571 7.566 7.543 7.539 7.513 7.450 7.448 7.444 7.428 7.424 7.422 7.260 7.206 7.191 7.179 7.164 5.526



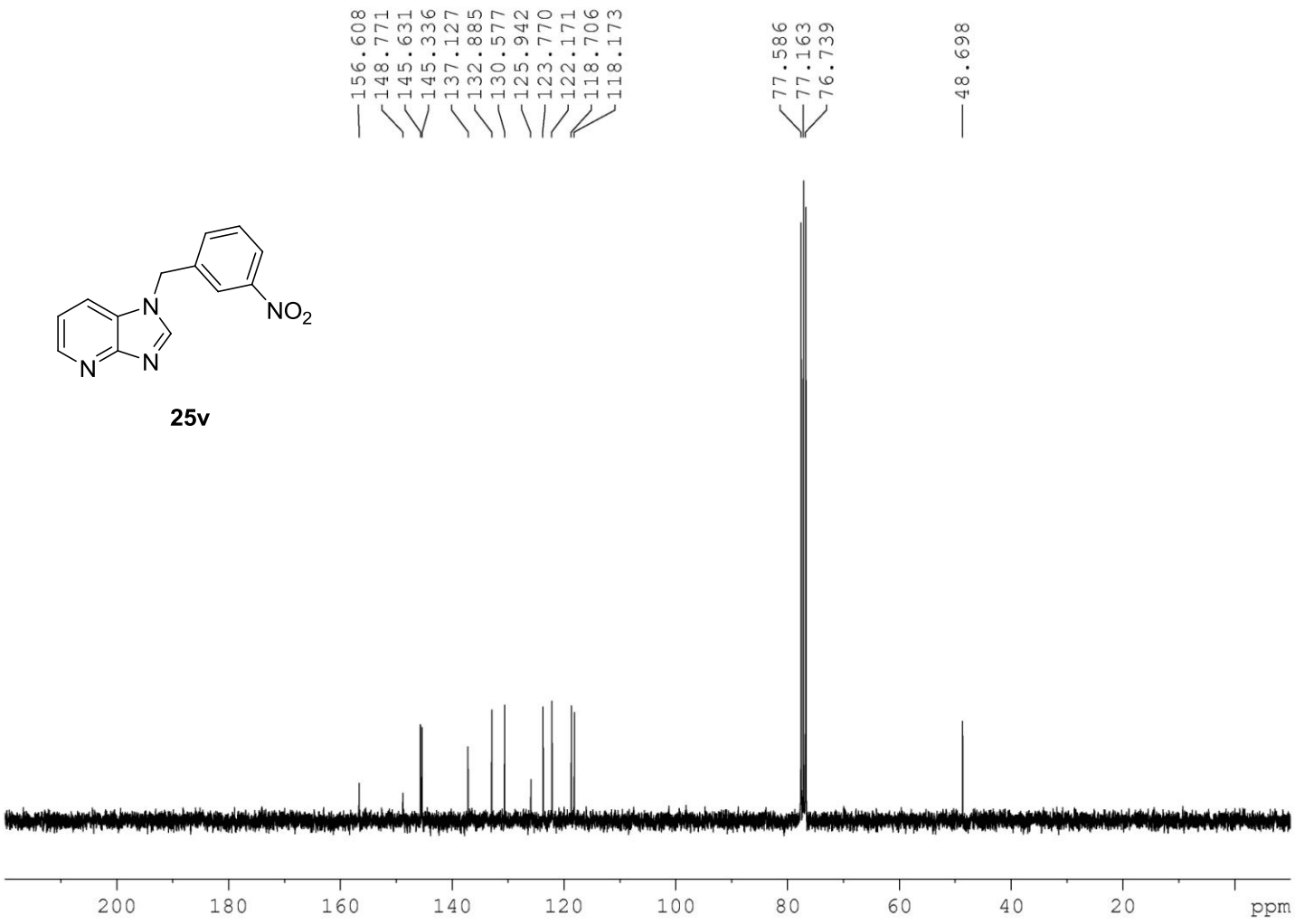
25v



BRUKER

NAME	AJR-5-290	
EXPNO	3	
PROCNO	1	
Date_	20130324	
Time	14.45	
INSTRUM	spect	
PROBHD	5 mm QNP 1H/1	
PULPROG	zg	
TD	32768	
SOLVENT	CDCl3	
NS	16	
DS	0	
SWH	3591.954	Hz
FIDRES	0.109618	Hz
AQ	4.5613556	sec
RG	80.6	
DW	139.200	usec
DE	54.00	usec
TE	298.2	K
D1	5.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	9.75	usec
PL1	0.00	dB
SFO1	300.1315007	MHz
SI	32768	
SF	300.1300062	MHz
WDW	EM	
SSB	0	
LB	0.20	Hz
GB	0	
PC	1.00	

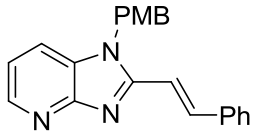
AJR-5-290


156.608
148.771
145.631
145.336
137.127
132.885
130.577
125.942
123.770
122.171
118.706
118.173
77.586
77.163
76.739
48.698
NO2
N
N
N
200
180
160
140
120
100
80
60
40
20
ppm

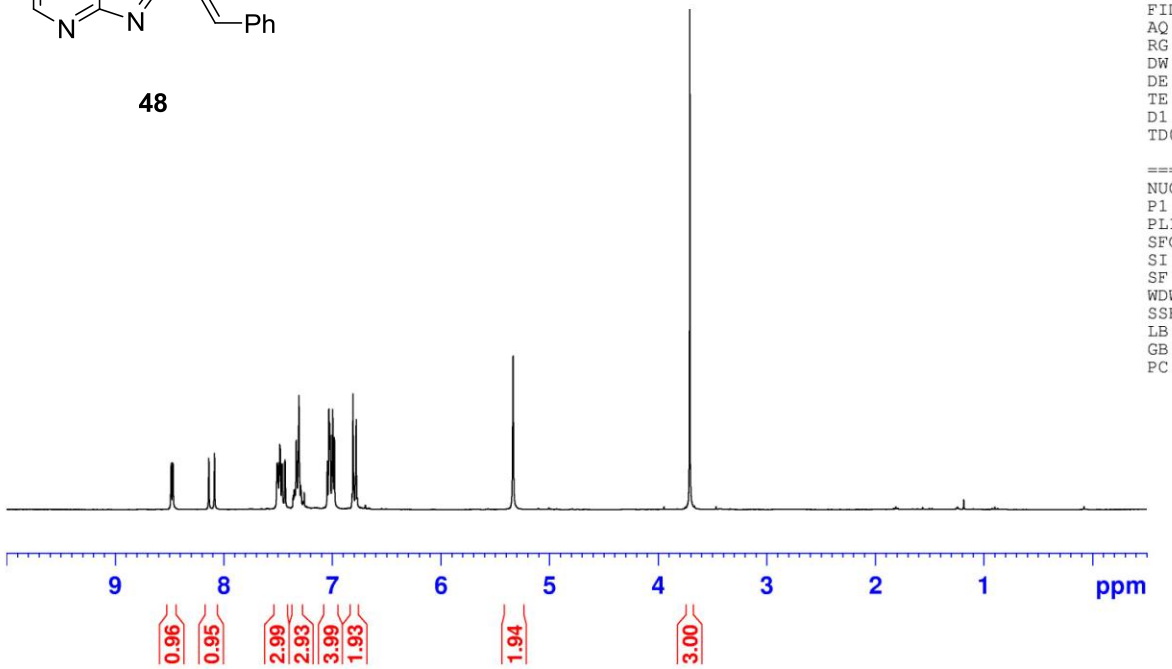
25v

AJR-5-277
Post Column & Pump

8.140 8.087 7.512 7.506 7.486 7.481 7.466 7.462 7.440 7.435 7.334 7.316 7.310 7.048 7.035 7.028 7.022 7.006 6.998 6.983 6.811 6.804 6.782 5.338 3.710



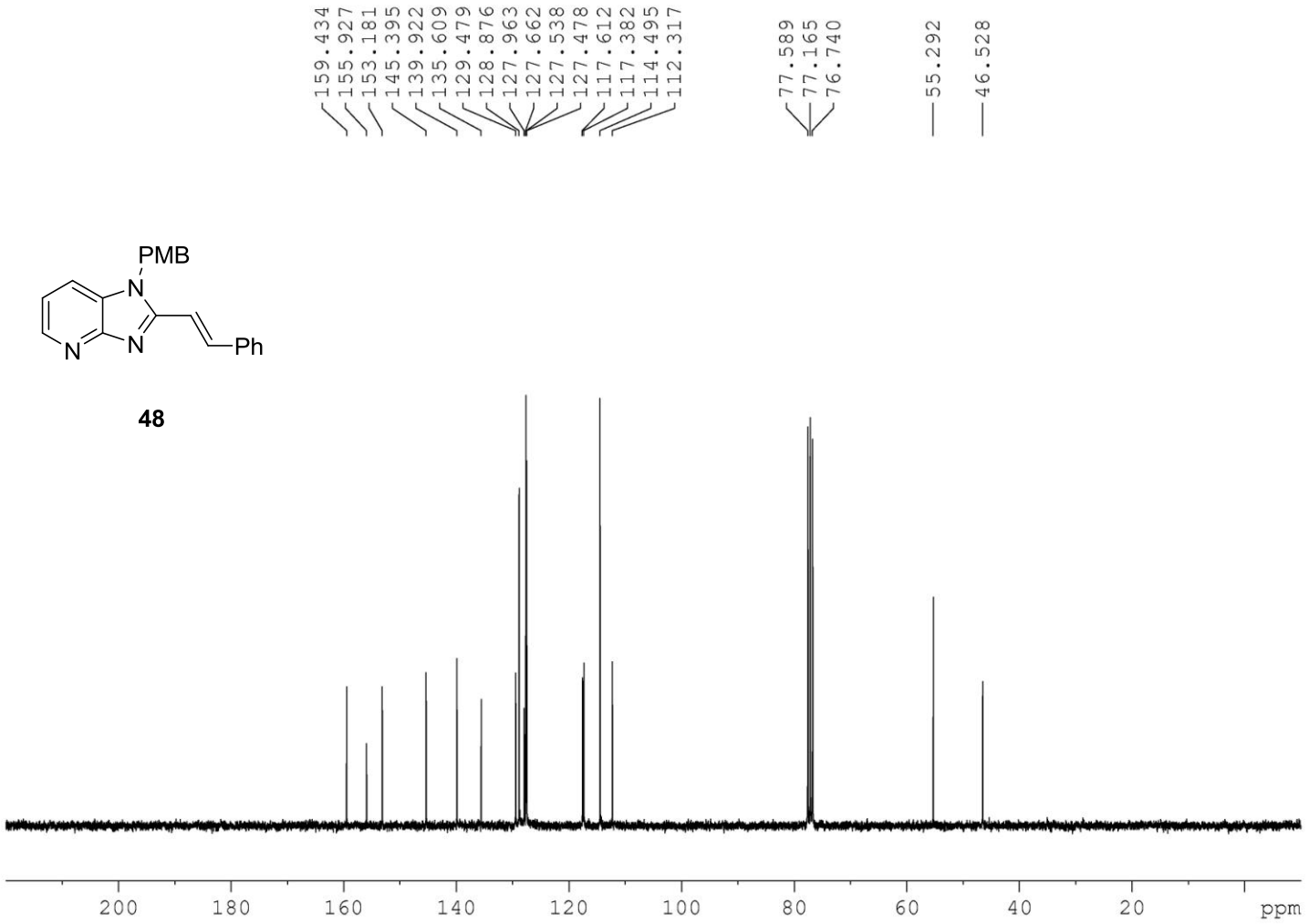
48



BRUKER

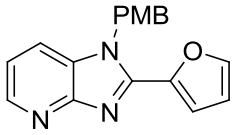
NAME	AJR-5-277
EXPNO	3
PROCNO	1
Date_	20130123
Time	9.36
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	64
DW	139.200 usec
DE	54.00 usec
TE	297.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300061 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

AJR-5-277


159.434
155.927
153.181
145.395
139.922
135.609
129.479
128.876
127.963
127.662
127.538
127.478
117.612
117.382
114.495
112.317
77.589
77.165
76.740
55.292
46.528
PMB
N
N
N
Ph
48
200
180
160
140
120
100
80
60
40
20
ppm

AJR-6-015
Post Column

7.574
7.572
7.540
7.535
7.513
7.508
7.294
7.291
7.282
7.279
7.260
7.103
7.087
7.076
7.060
7.051
7.036
7.029
6.799
6.792
6.777
6.770
6.574
6.568
6.563
6.557
5.636
3.717



46

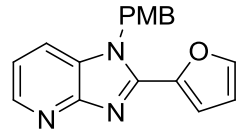
NAME	AJR-6-015
EXPNO	3
PROCNO	1
Date_	20130328
Time	15.24
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	181
DW	139.200 usec
DE	54.00 usec
TE	298.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300059 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

AJR-6-195

159.230
155.538
145.993
145.389
144.916
144.639
144.350
128.042
127.761
127.745
118.131
118.025
114.925
114.281
112.320

77.584
77.159
76.734

55.220
48.176

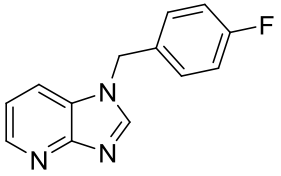


46

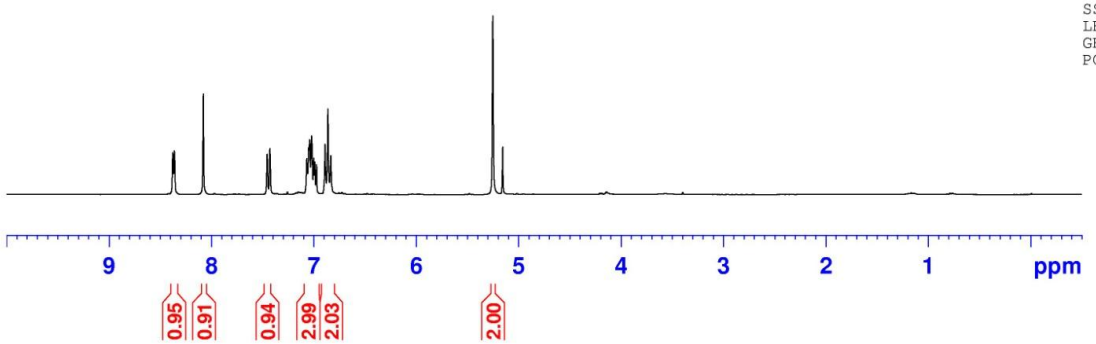
9.3 SNAR

TW-1-68
after column

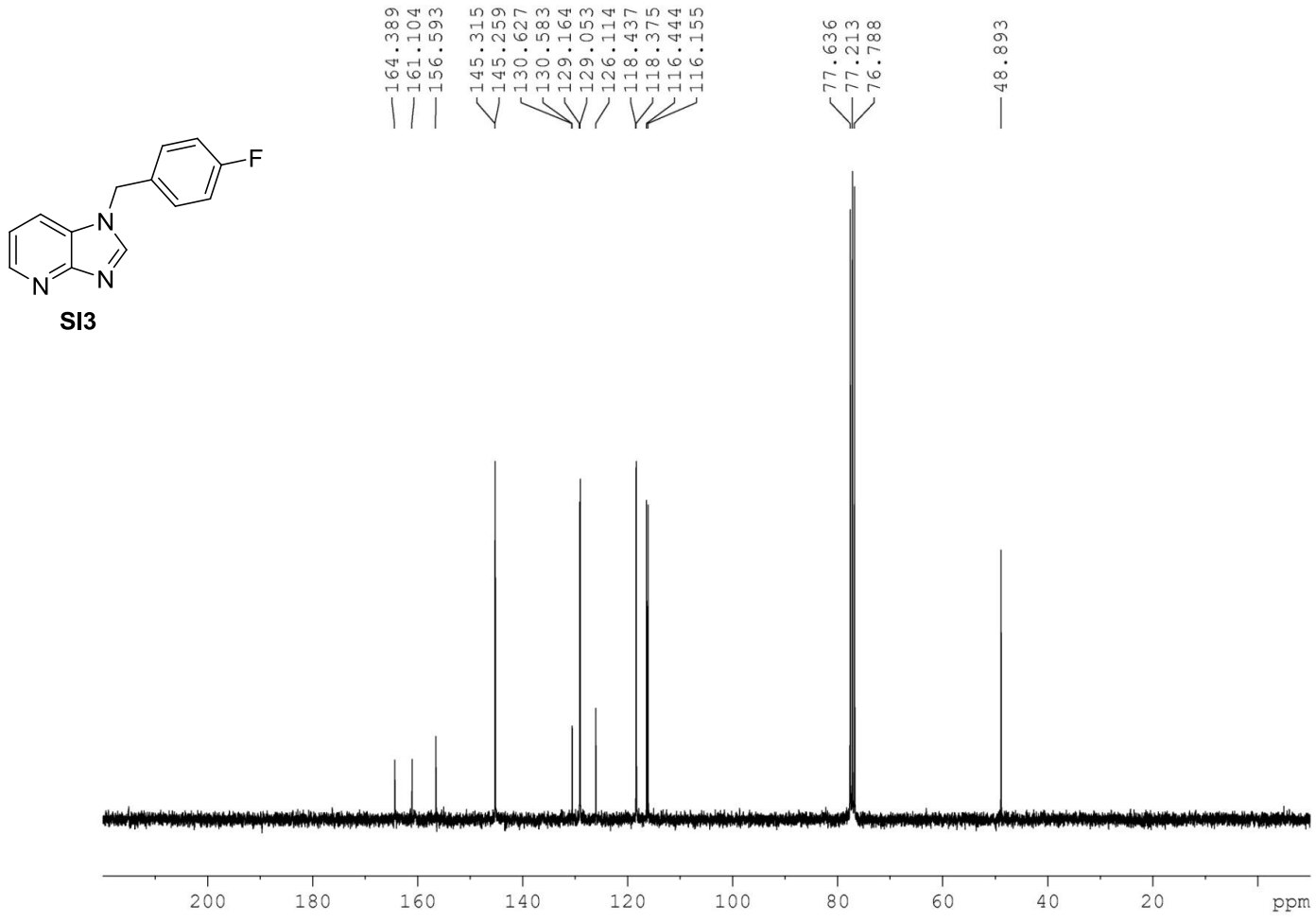
8.380
8.364
8.081
7.458
7.431
7.071
7.053
7.043
7.024
7.003
6.992
6.976
6.892
6.864
6.835
5.254
5.157

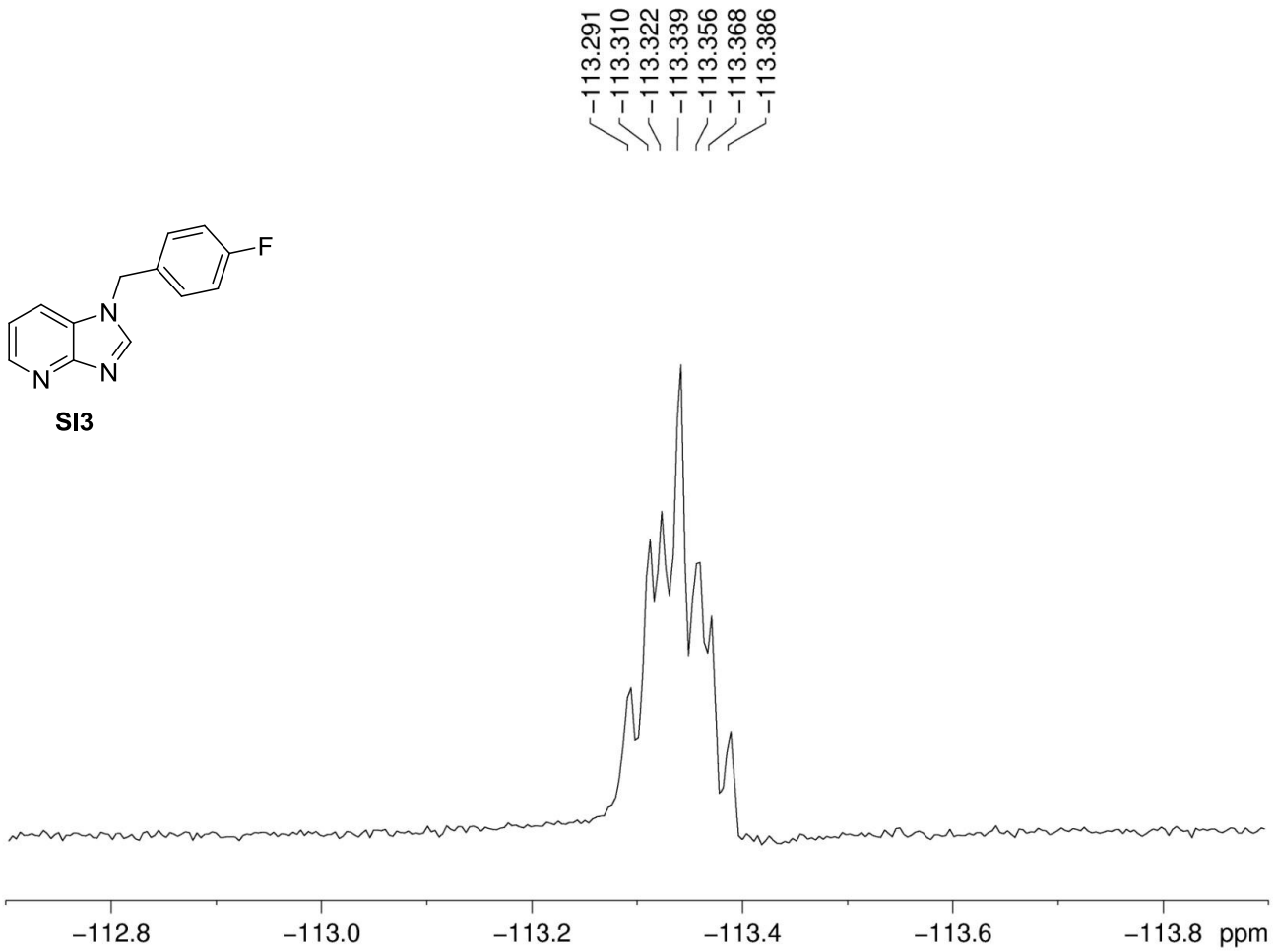


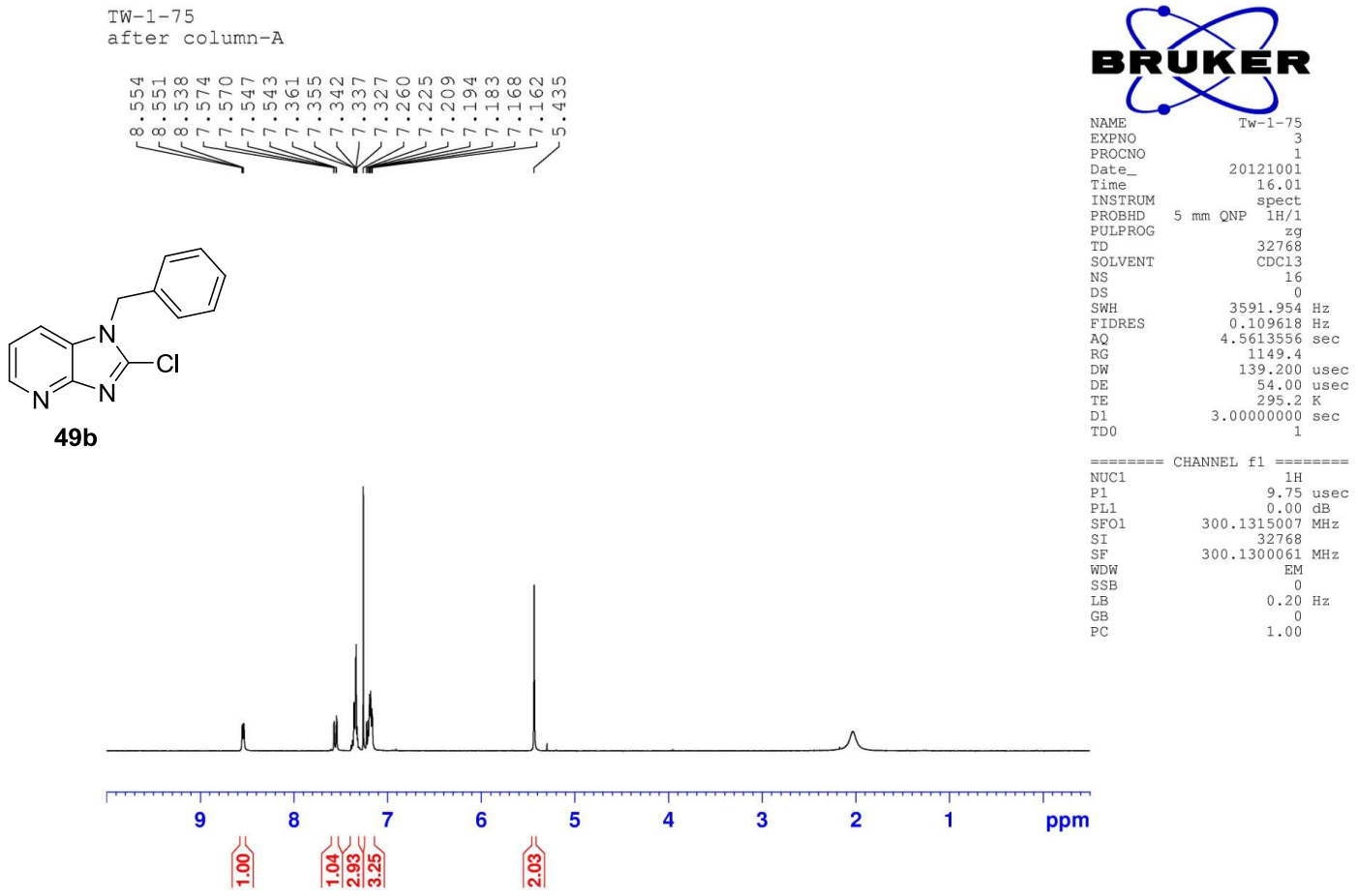
SI3



NAME	Tw-1-67
EXPNO	2
PROCNO	1
Date_	20120731
Time	15.39
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	40.3
DW	139.200 usec
DE	54.00 usec
TE	295.2 K
D1	3.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300062 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00


164.389
161.104
156.593
145.315
145.259
130.627
130.583
129.164
129.053
126.114
118.437
118.375
116.444
116.155
77.636
77.213
76.788
48.893
F
N
N
N
SI3
200
180
160
140
120
100
80
60
40
20
ppm


−113.291
−113.310
−113.322
−113.339
−113.356
−113.368
−113.386
F
N
N
N
SI3
−112.8
−113.0
−113.2
−113.4
−113.6
−113.8
ppm

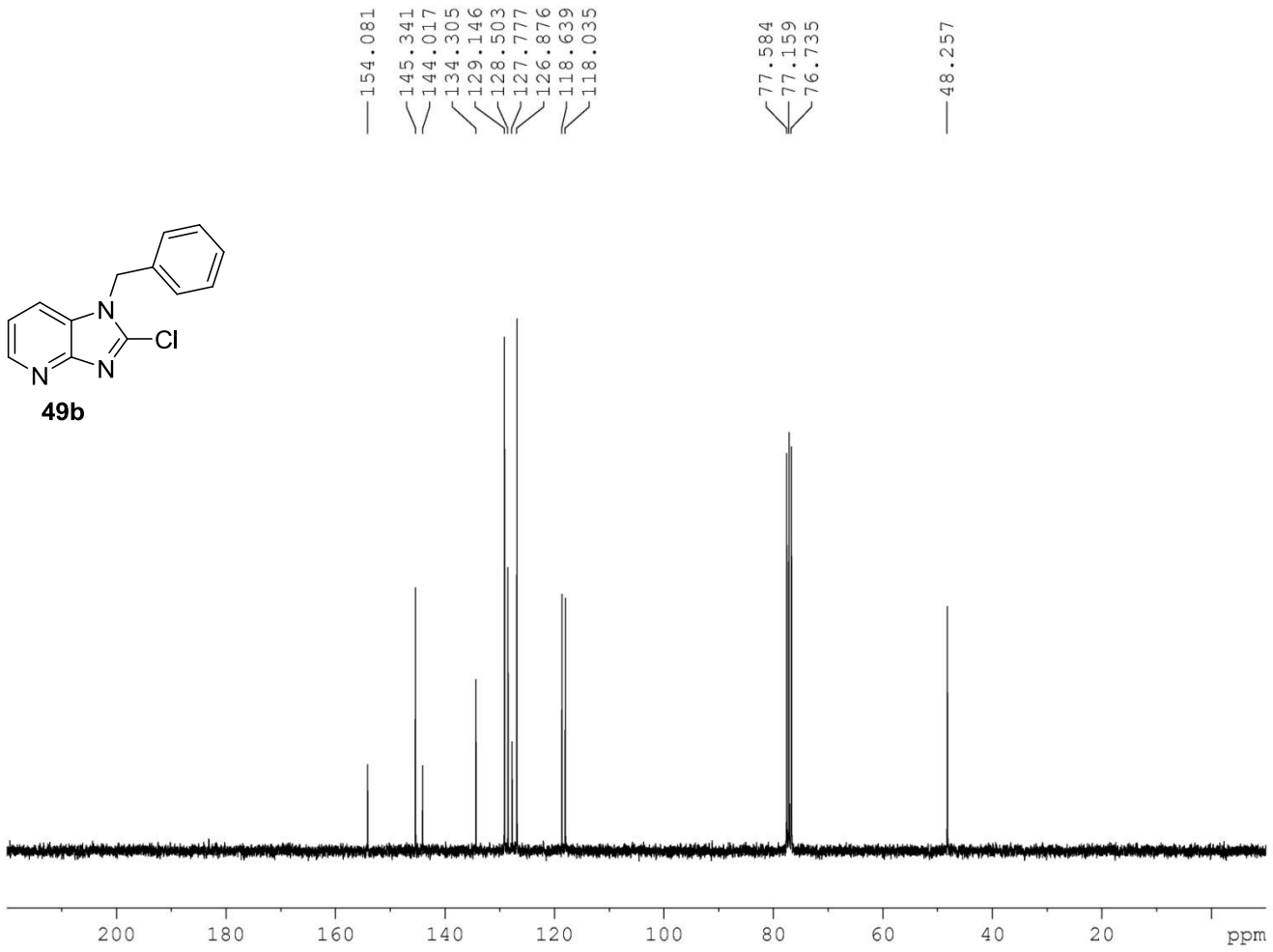


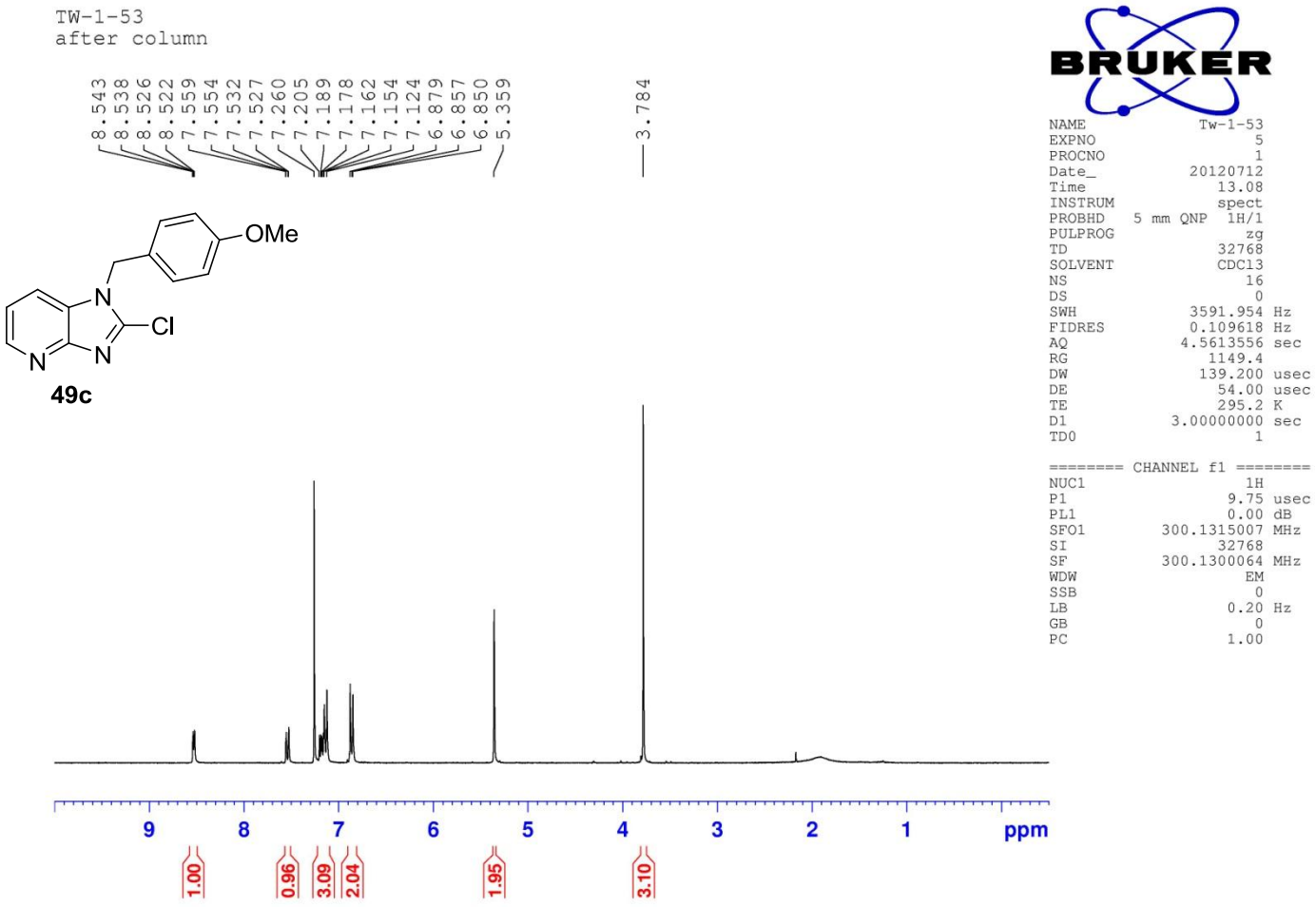
BRUKER

NAME	Tw-1-75
EXPNO	3
PROCNO	1
Date_	20121001
Time	16.01
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	1149.4
DW	139.200 usec
DE	54.00 usec
TE	295.2 K
D1	3.00000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300061 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00


154.081
145.341
144.017
134.305
129.146
128.503
127.777
126.876
118.639
118.035
77.584
77.159
76.735
48.257
N
Cl
N
N
49b
200
180
160
140
120
100
80
60
40
20
ppm

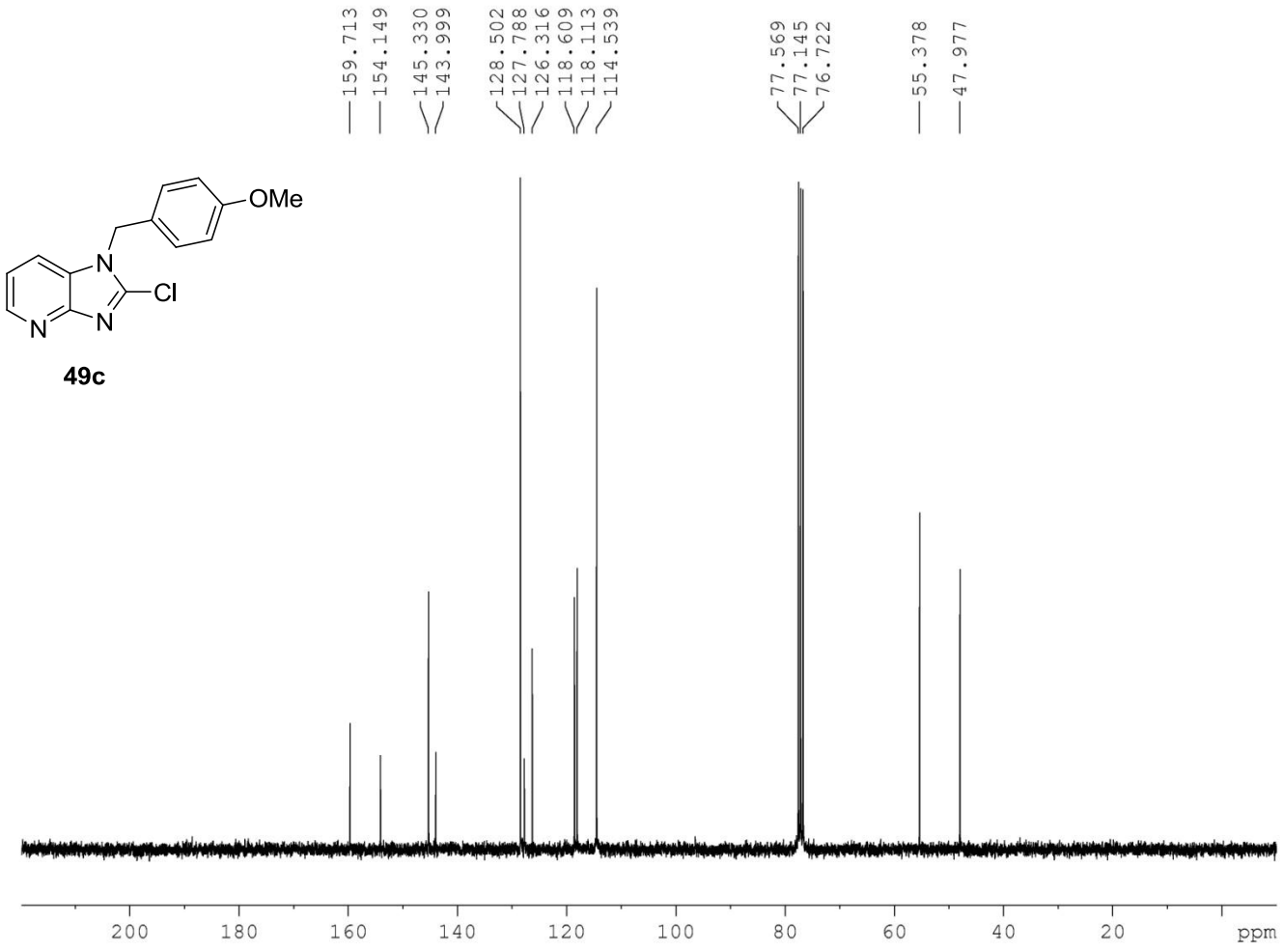


BRUKER

NAME	Tw-1-53
EXPNO	5
PROCNO	1
Date_	20120712
Time	13.08
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	1149.4
DW	139.200 usec
DE	54.00 usec
TE	295.2 K
D1	3.00000000 sec
TD0	1

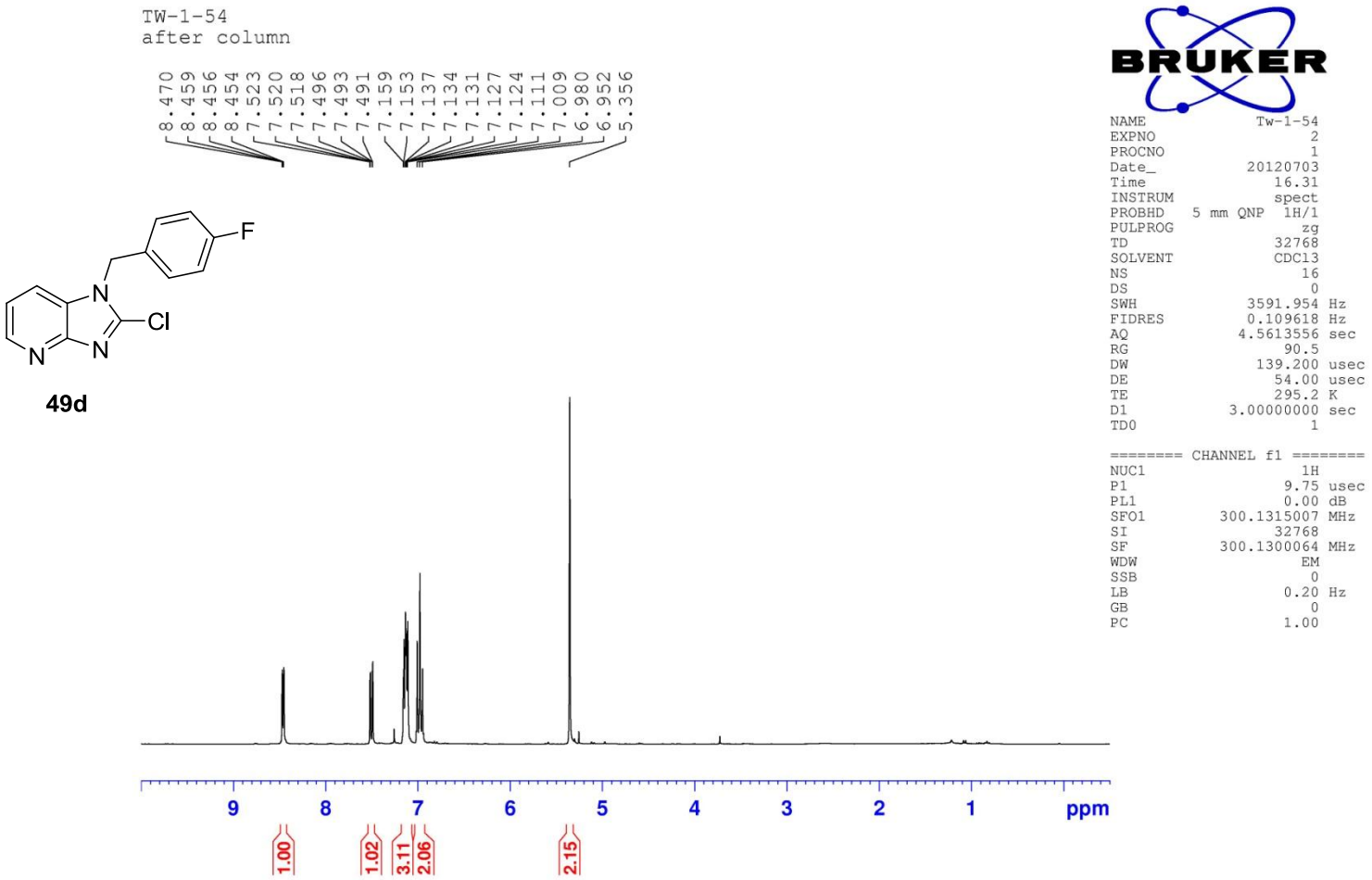
======== CHANNEL f1 ========

NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300064 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00


159.713
154.149
145.330
143.999
128.502
127.788
126.316
118.609
118.113
114.539
77.569
77.145
76.722
55.378
47.977
OMe
N
Cl
N
N
200
180
160
140
120
100
80
60
40
20
ppm

49c

\

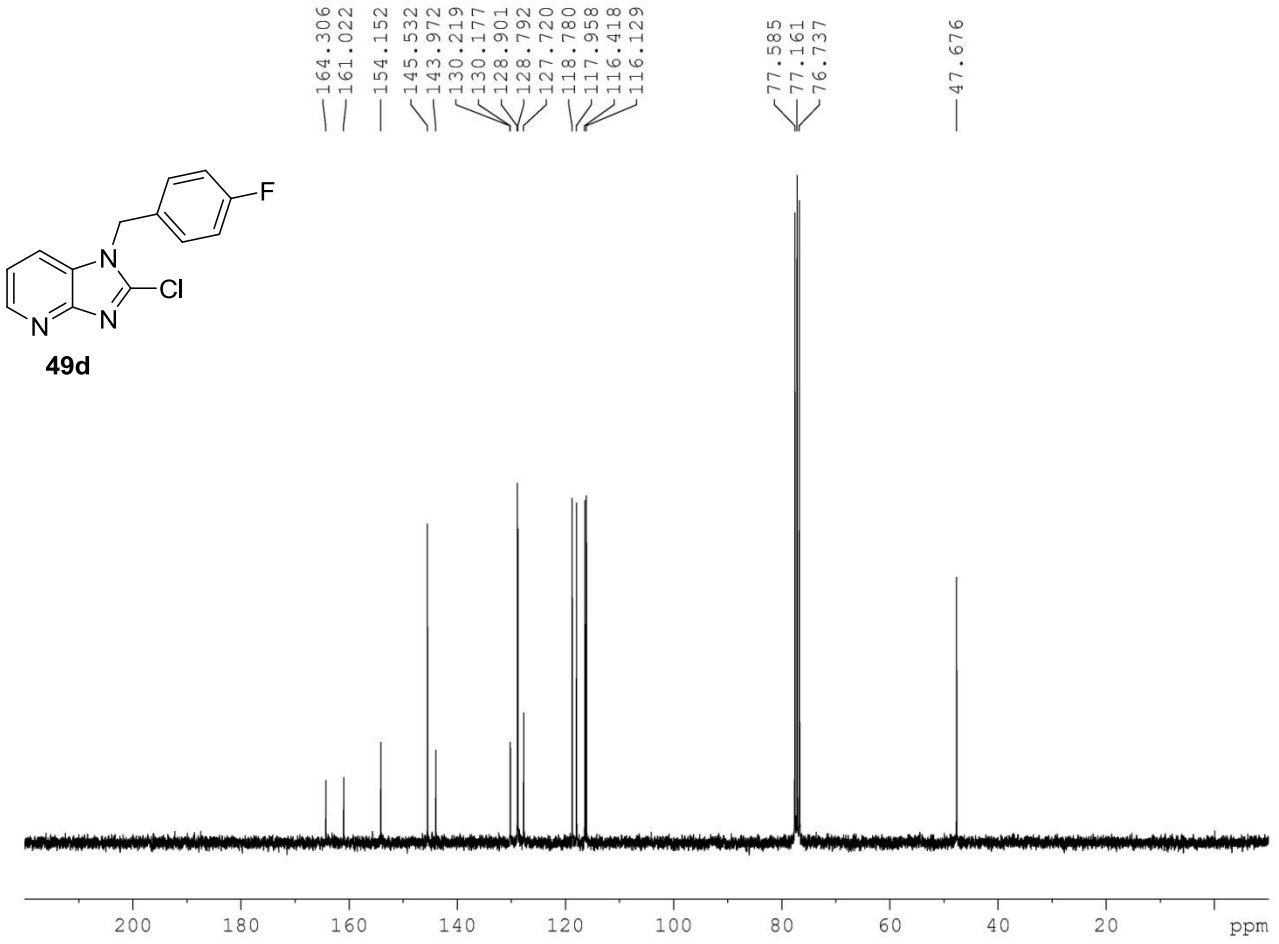


BRUKER

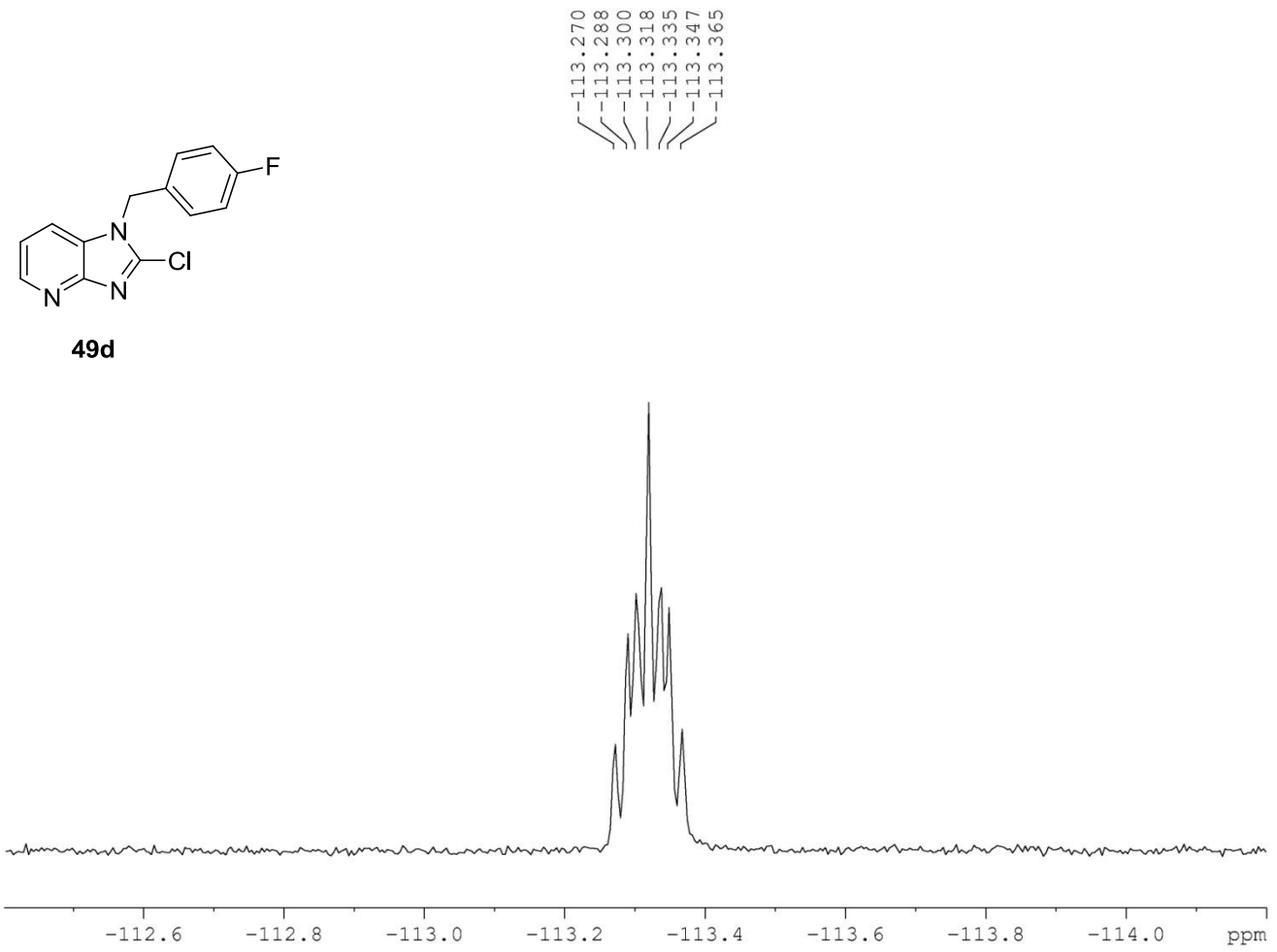
NAME	Tw-1-54
EXPNO	2
PROCNO	1
Date_	20120703
Time	16.31
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	90.5
DW	139.200 usec
DE	54.00 usec
TE	295.2 K
D1	3.00000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300064 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

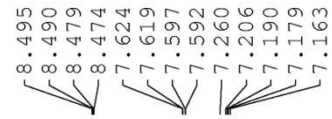

164.306
161.022
154.152
145.532
143.972
130.219
130.177
128.901
128.792
127.720
118.780
117.958
116.418
116.129
77.585
77.161
76.737
47.676
F
N
Cl
N
N
200
180
160
140
120
100
80
60
40
20
ppm

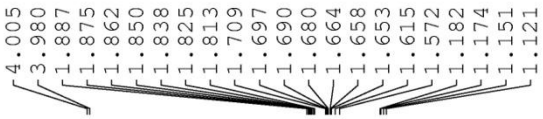
49d

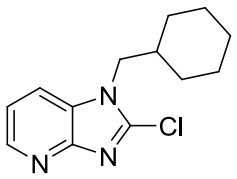

-113.270
-113.288
-113.300
-113.318
-113.335
-113.347
-113.365
F
N
Cl
N
N
-112.6
-112.8
-113.0
-113.2
-113.4
-113.6
-113.8
-114.0
ppm

49d

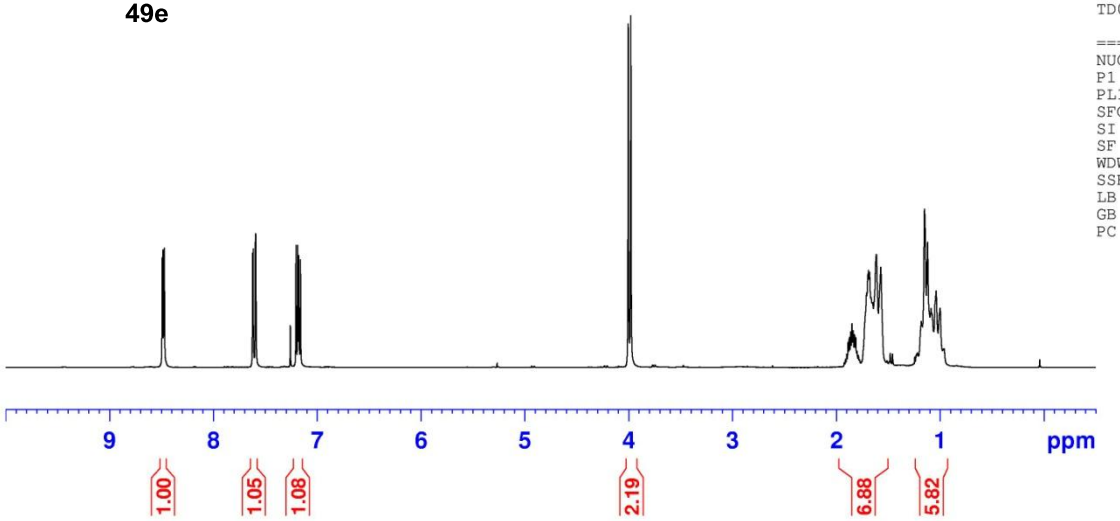
TW-1-62
after column



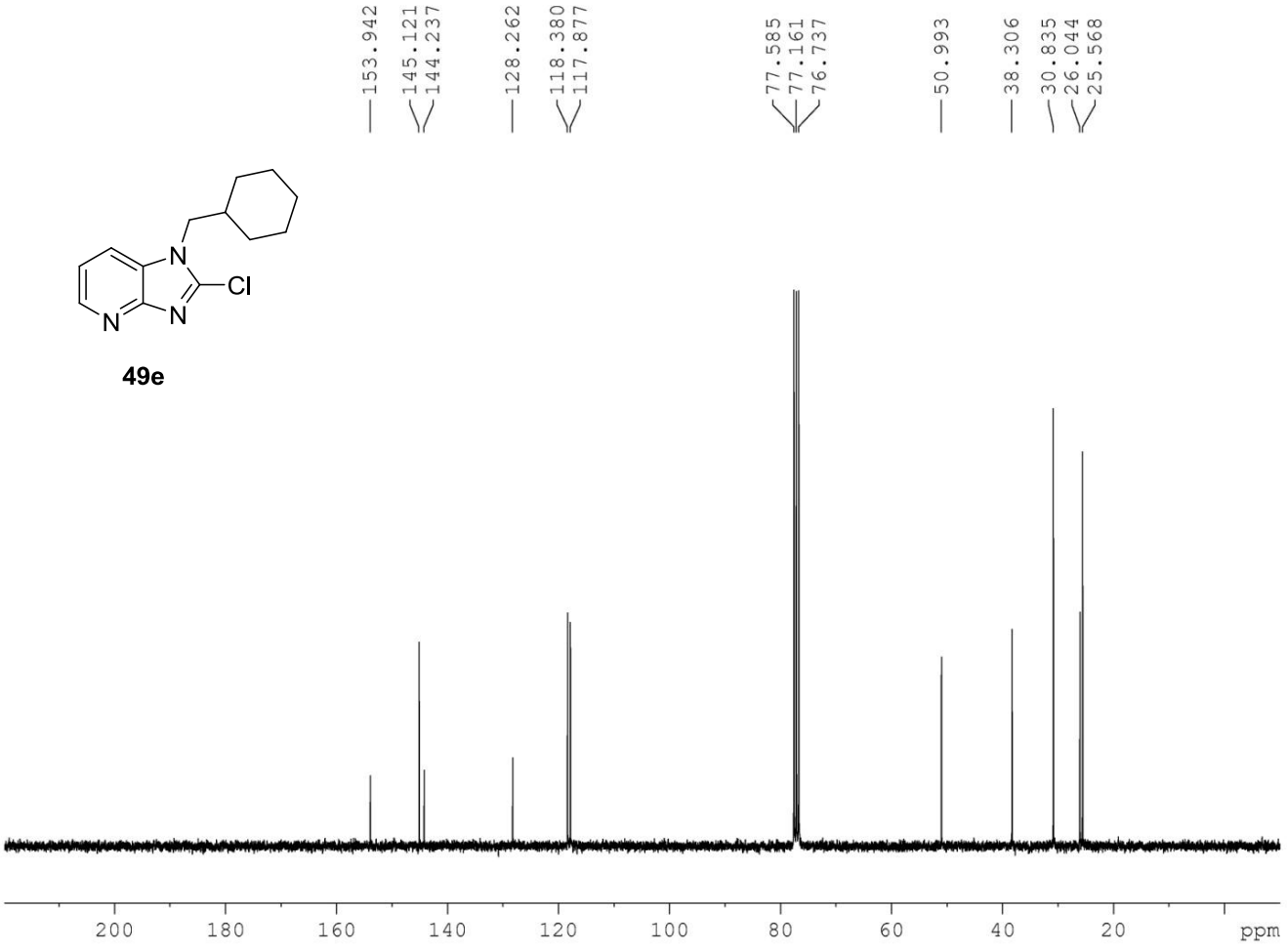




49e

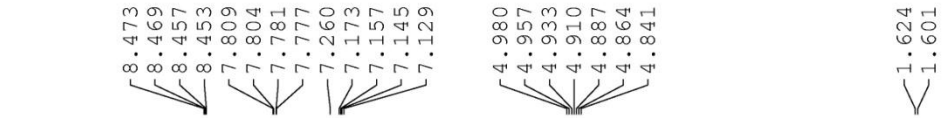


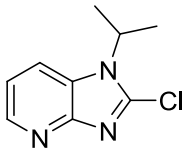
NAME	Tw-1-62	
EXPNO	4	
PROCNO	1	
Date_	20120717	
Time	15.44	
INSTRUM	spect	
PROBHD	5 mm QNP 1H/1	
PULPROG	zg	
TD	32768	
SOLVENT	CDCl3	
NS	16	
DS	0	
SWH	3591.954	Hz
FIDRES	0.109618	Hz
AQ	4.5613556	sec
RG	64	
DW	139.200	usec
DE	54.00	usec
TE	295.2	K
D1	3.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	9.75	usec
PL1	0.00	dB
SFO1	300.1315007	MHz
SI	32768	
SF	300.1300063	MHz
WDW	EM	
SSB	0	
LB	0.20	Hz
GB	0	
PC	1.00	


153.942
145.121
144.237
128.262
118.380
117.877
77.585
77.161
76.737
50.993
38.306
30.835
26.044
25.568
N
Cl
N
N
200
180
160
140
120
100
80
60
40
20
ppm

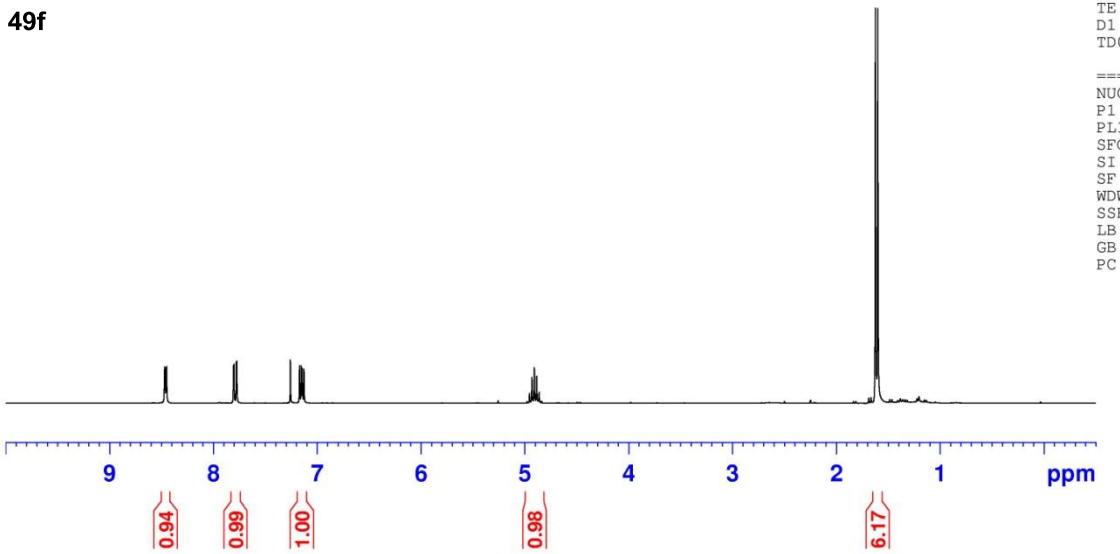
49e

AJ-1-63
after column

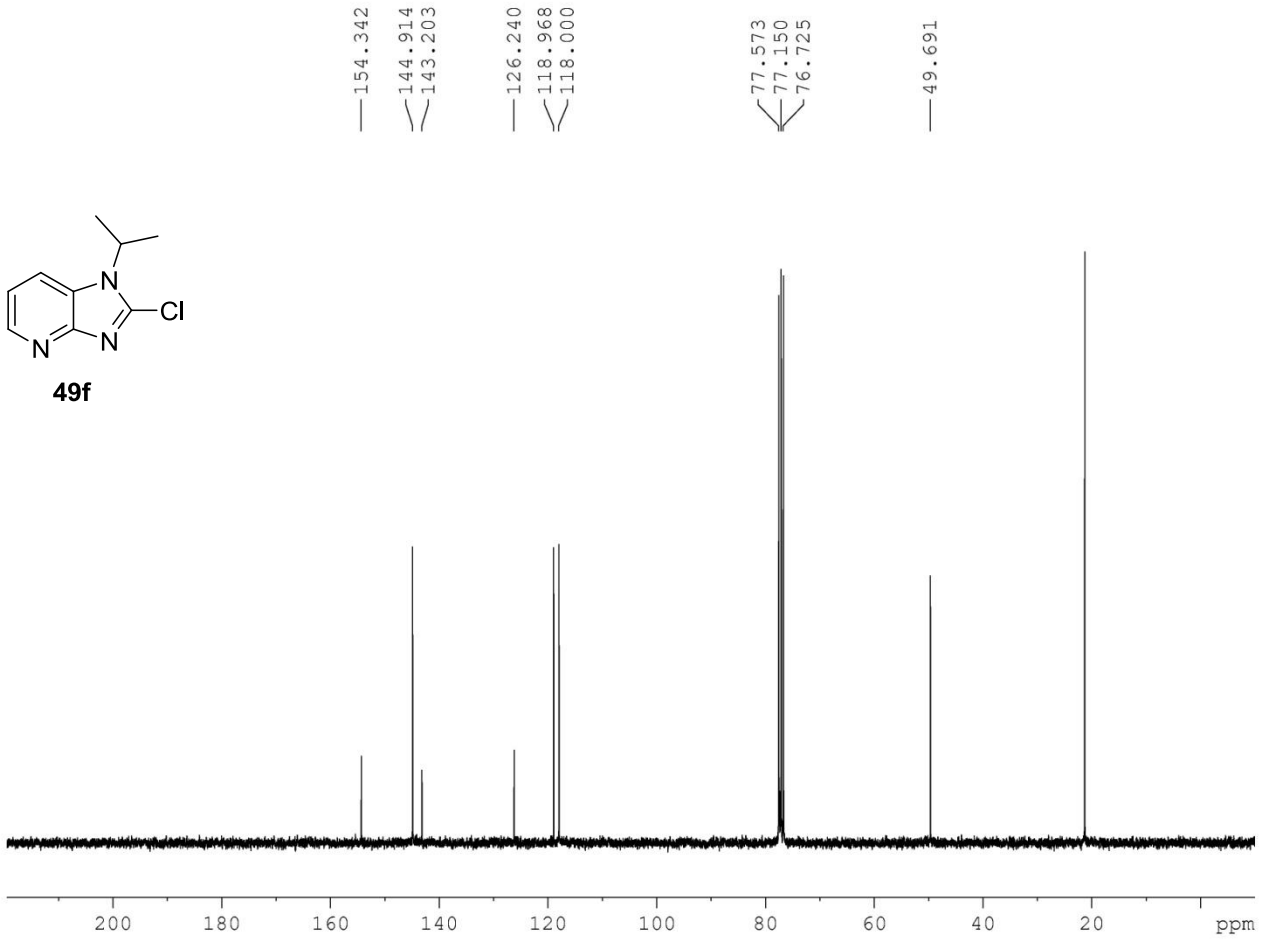




49f

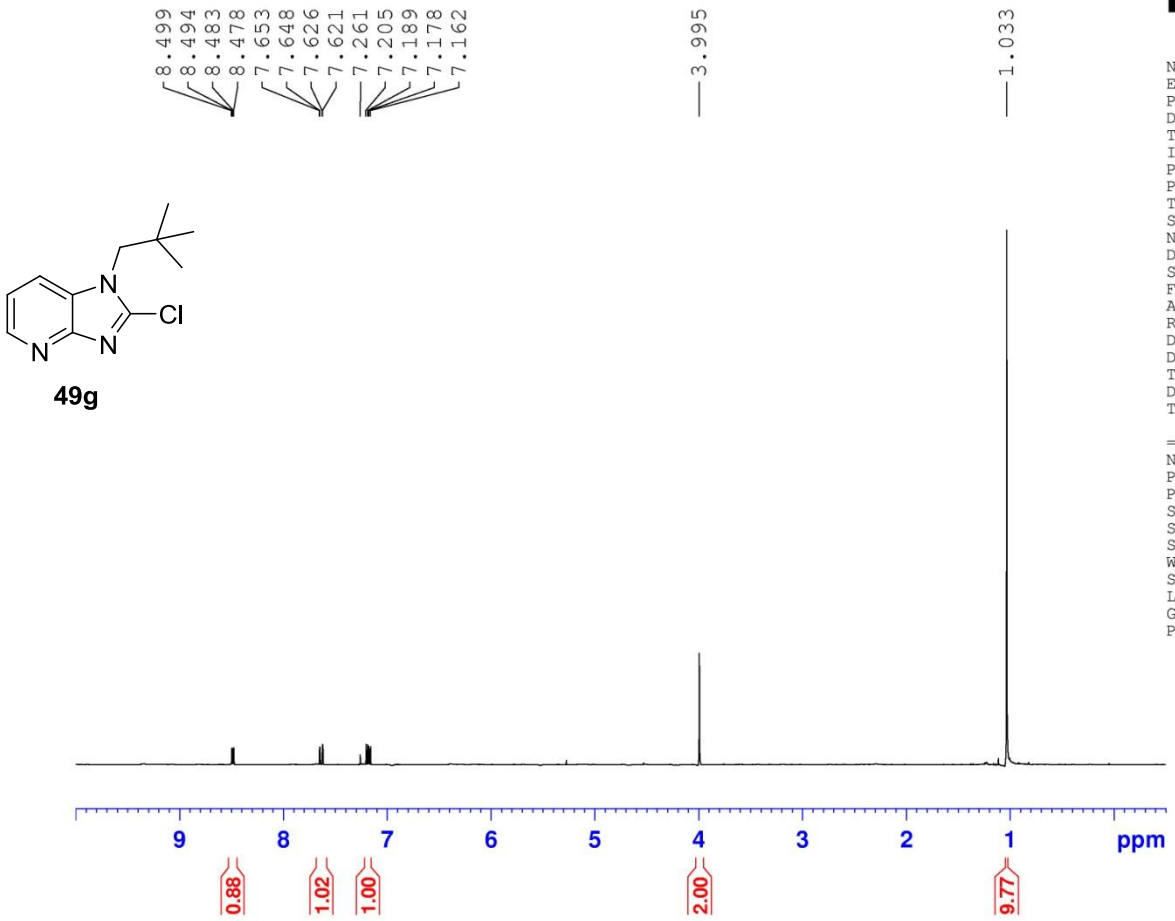


NAME	AJ-1-63
EXPNO	2
PROCNO	1
Date_	20120720
Time	8.51
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	228.1
DW	139.200 usec
DE	54.00 usec
TE	683.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300063 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00


154.342
144.914
143.203
126.240
118.968
118.000
77.573
77.150
76.725
49.691
N
N
Cl
N
200
180
160
140
120
100
80
60
40
20
ppm

49f

AJ-1-59
after column



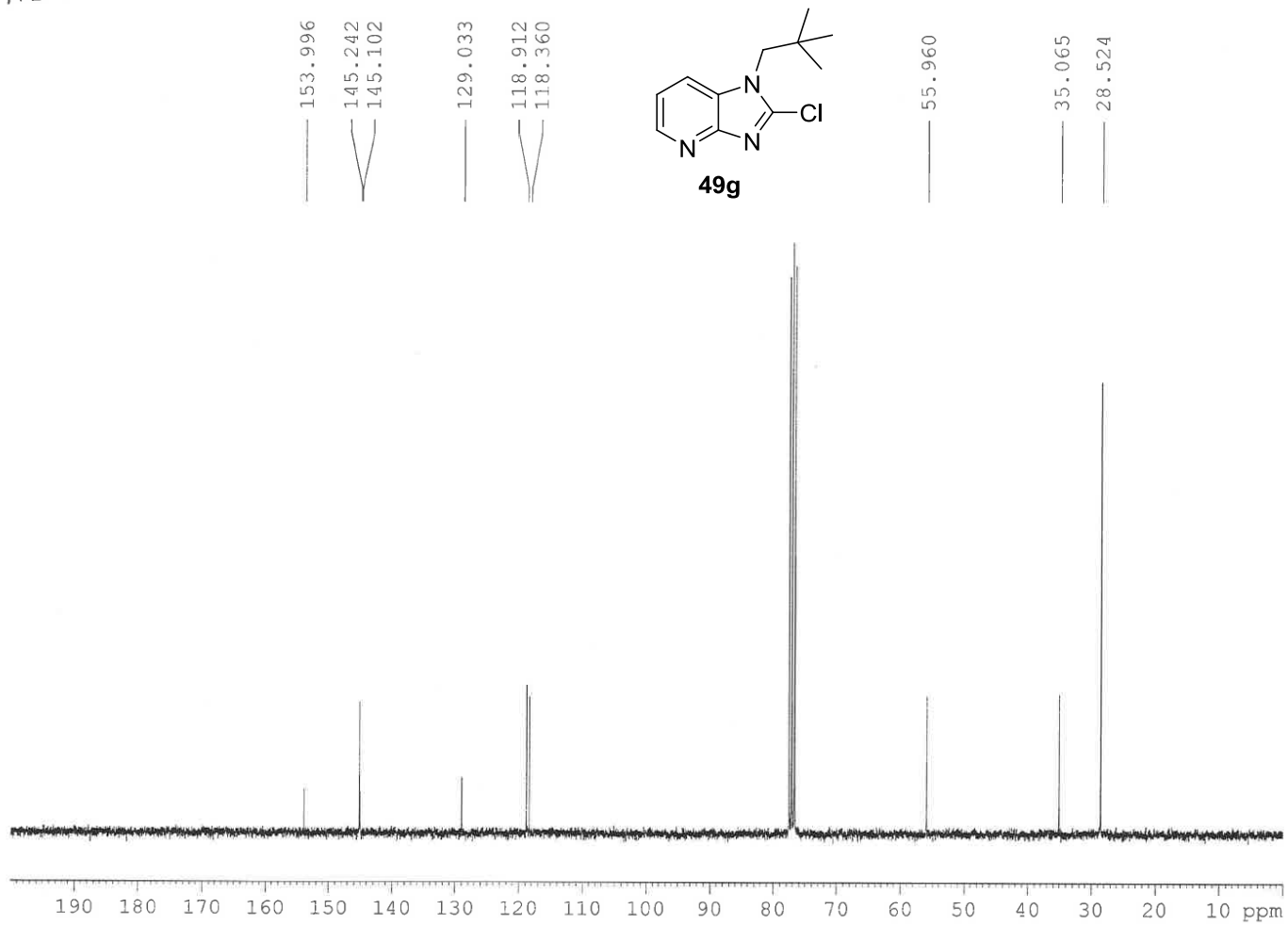
49g

BRUKER

NAME	AJ-1-59	
EXPNO	1	
PROCNO	1	
Date_	20120712	
Time	17.12	
INSTRUM	spect	
PROBHD	5 mm QNP 1H/1	
PULPROG	zg	
TD	32768	
SOLVENT	CDCl3	
NS	16	
DS	0	
SWH	3591.954	Hz
FIDRES	0.109618	Hz
AQ	4.5613556	sec
RG	574.7	
DW	139.200	usec
DE	54.00	usec
TE	295.2	K
D1	5.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	9.75	usec
PL1	0.00	dB
SFO1	300.1315007	MHz
SI	32768	
SF	300.1300061	MHz
WDW	EM	
SSB	0	
LB	0.20	Hz
GB	0	
PC	1.00	

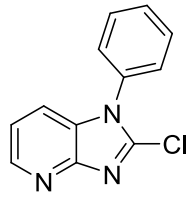
\

AJ-1-59

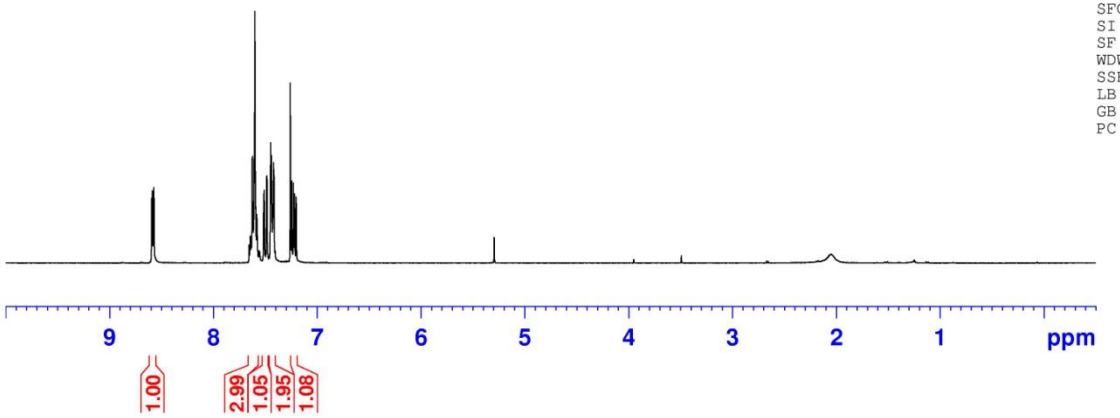

153.996
145.242
145.102
129.033
118.912
118.360
55.960
35.065
28.524
N
Cl
N
N
49g
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

AJ-1-65
after column

7.622
7.615
7.610
7.603
7.597
7.593
7.585
7.580
7.518
7.512
7.490
7.485
7.450
7.443
7.436
7.431
7.429
7.423
7.418
7.261
7.247
7.231
7.220
7.204

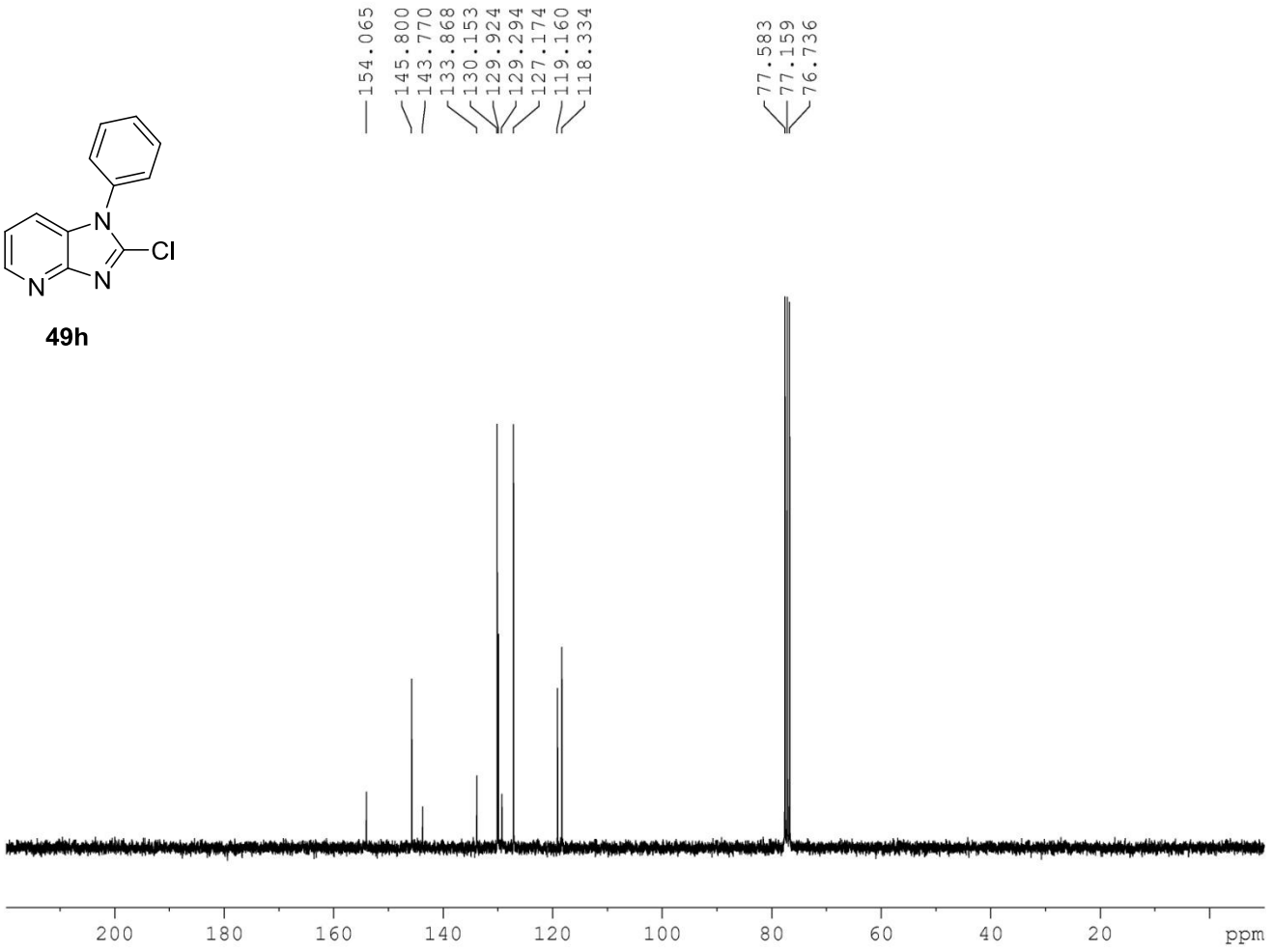


49h

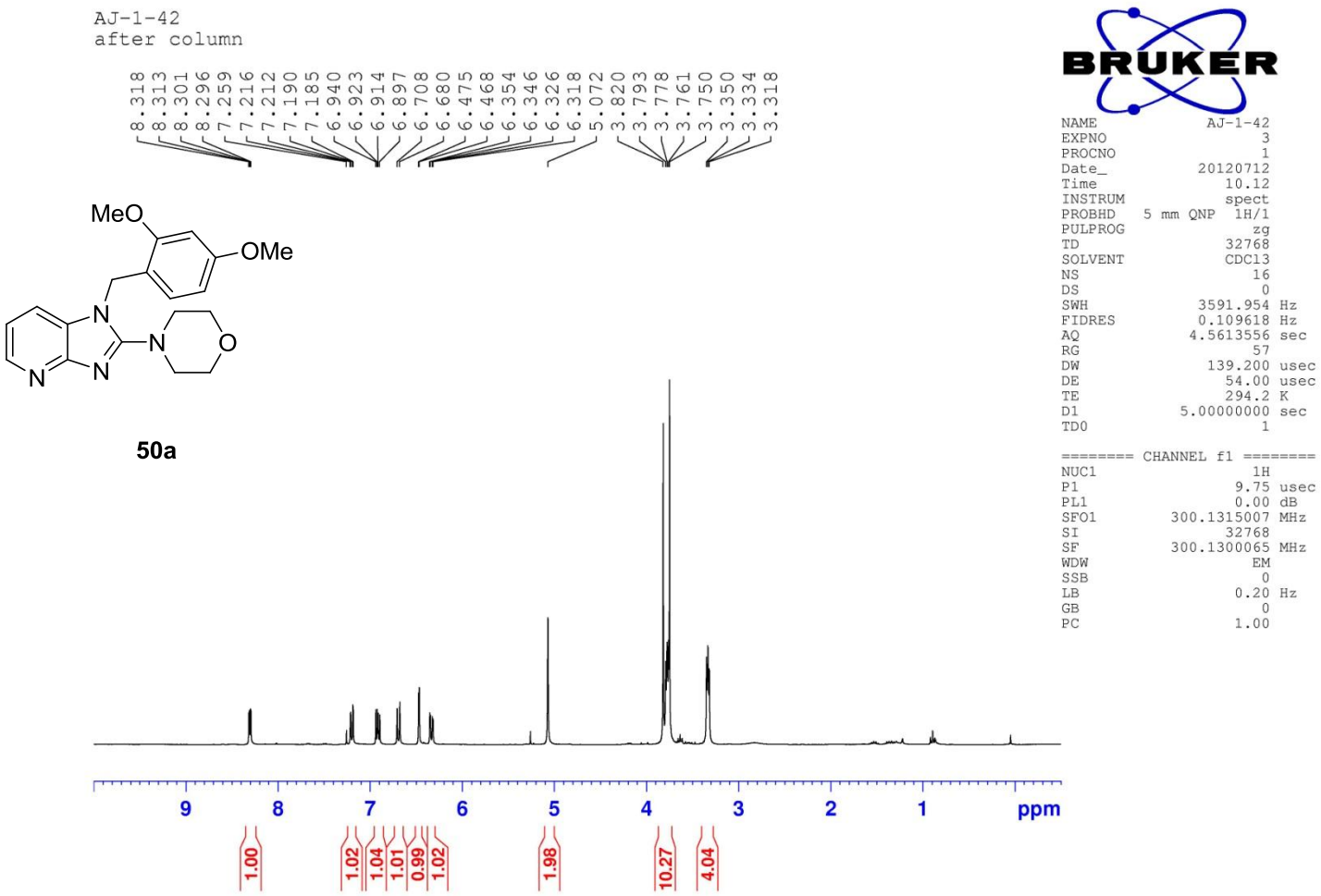


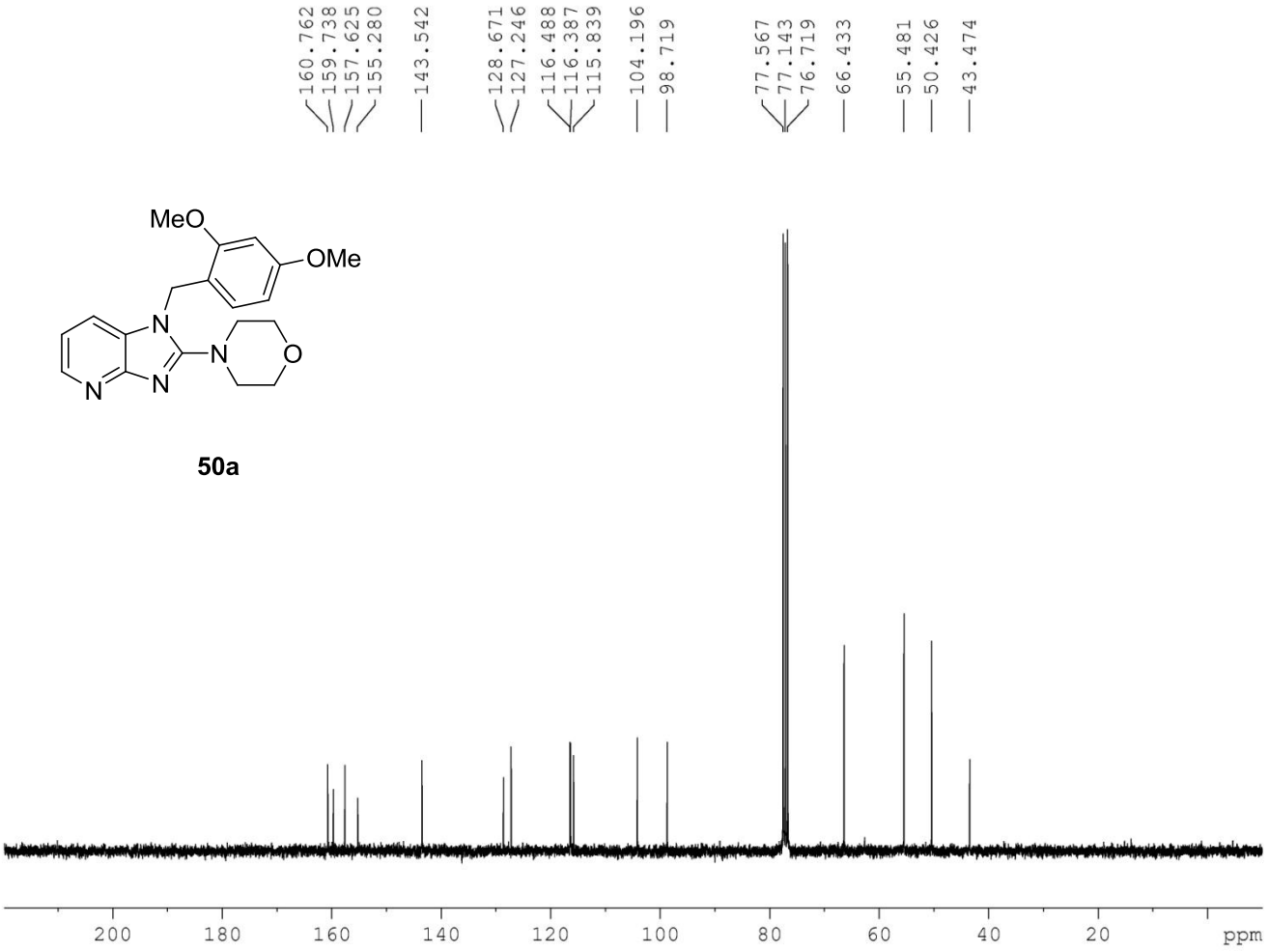
BRUKER

NAME	AJ-1-65	
EXPNO	1	
PROCNO	1	
Date_	20120726	
Time	16.19	
INSTRUM	spect	
PROBHD	5 mm QNP 1H/1	
PULPROG	zg	
TD	32768	
SOLVENT	CDCl3	
NS	12	
DS	0	
SWH	3591.954	Hz
FIDRES	0.109618	Hz
AQ	4.5613556	sec
RG	574.7	
DW	139.200	usec
DE	54.00	usec
TE	295.2	K
D1	5.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	9.75	usec
PL1	0.00	dB
SFO1	300.1315007	MHz
SI	32768	
SF	300.1300061	MHz
WDW	EM	
SSB	0	
LB	0.20	Hz
GB	0	
PC	1.00	


154.065
145.800
143.770
133.868
130.153
129.924
129.294
127.174
119.160
118.334
77.583
77.159
76.736
N
N
N
Cl
200
180
160
140
120
100
80
60
40
20
ppm

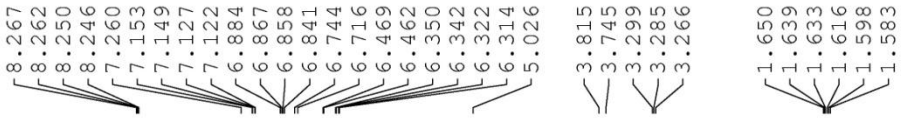
49h

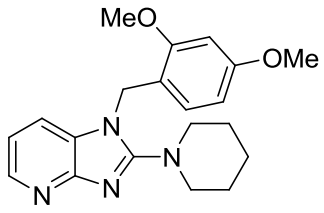

AJ-1-42
after column
8.318
8.313
8.301
8.296
7.259
7.216
7.212
7.190
7.185
6.940
6.923
6.914
6.897
6.708
6.680
6.475
6.468
6.354
6.346
6.326
6.318
5.072
3.820
3.793
3.778
3.761
3.750
3.350
3.334
3.318
MeO
OMe
N
N
N
O
N
50a
BRUKER
NAME AJ-1-42
EXPNO 3
PROCNO 1
Date_ 20120712
Time 10.12
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 16
DS 0
SWH 3591.954 Hz
FIDRES 0.109618 Hz
AQ 4.5613556 sec
RG 57
DW 139.200 usec
DE 54.00 usec
TE 294.2 K
D1 5.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.75 usec
PL1 0.00 dB
SFO1 300.1315007 MHz
SI 32768
SF 300.1300065 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00
9
8
7
6
5
4
3
2
1
ppm
1.00
1.02
1.04
1.01
0.99
1.02
1.98
10.27
4.04


160.762
159.738
157.625
155.280
143.542
128.671
127.246
116.488
116.387
115.839
104.196
98.719
77.567
77.143
76.719
66.433
55.481
50.426
43.474
MeO
OMe
N
N
N
N
O
200
180
160
140
120
100
80
60
40
20
ppm

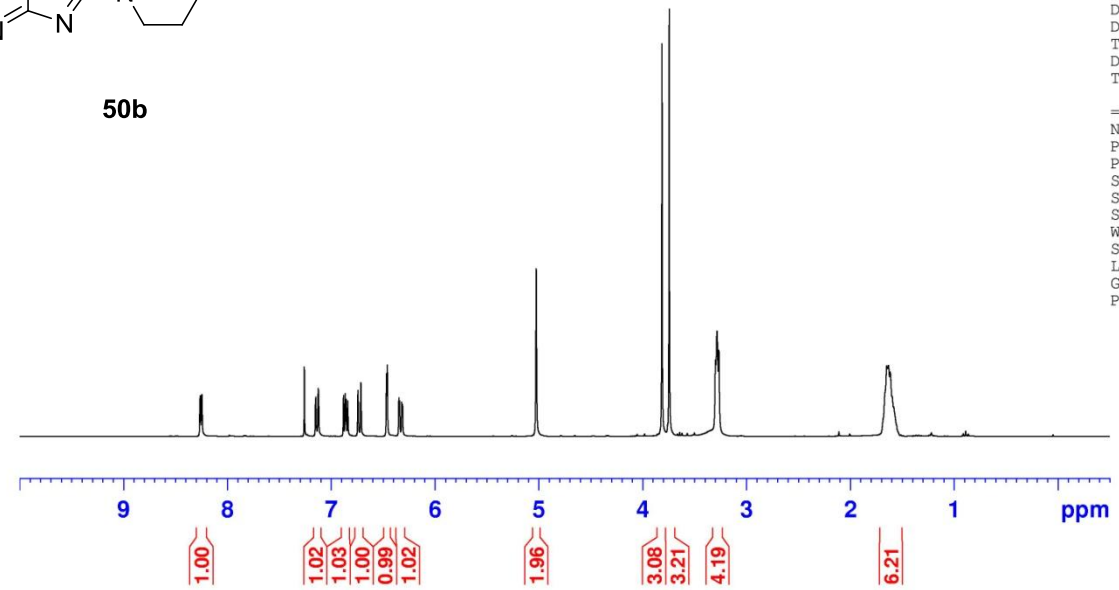
50a

AJR-5-033

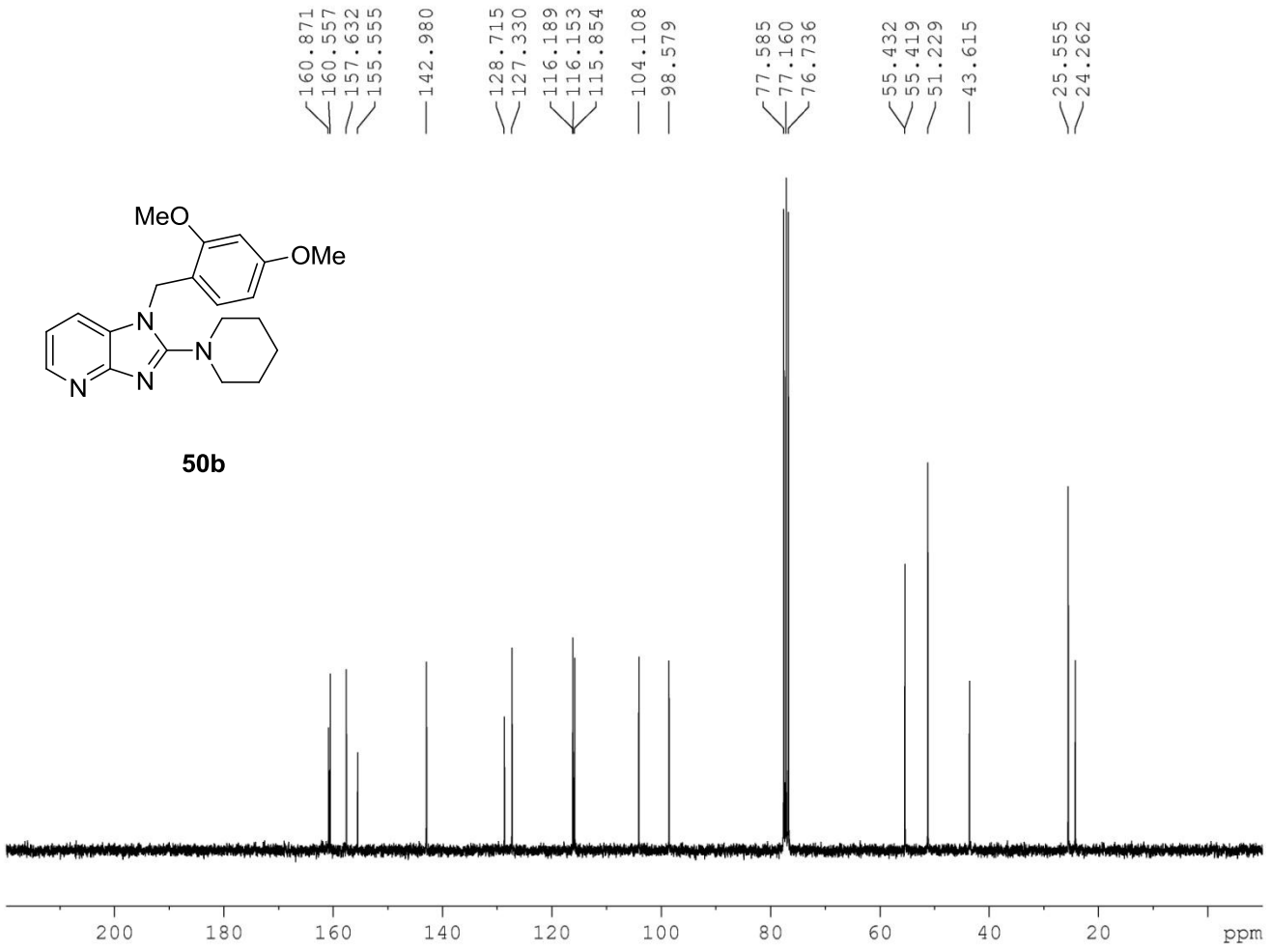




50b

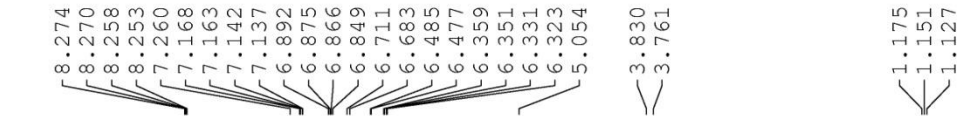


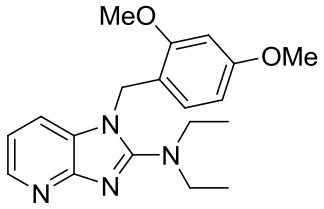
NAME	AJR-5-033
EXPNO	4
PROCNO	1
Date_	20120702
Time	18.51
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	57
DW	139.200 usec
DE	54.00 usec
TE	295.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300062 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00


160.871
160.557
157.632
155.555
142.980
128.715
127.330
116.189
116.153
115.854
104.108
98.579
77.585
77.160
76.736
55.432
55.419
51.229
43.615
25.555
24.262
MeO
OMe
N
N
N
N
200
180
160
140
120
100
80
60
40
20
ppm

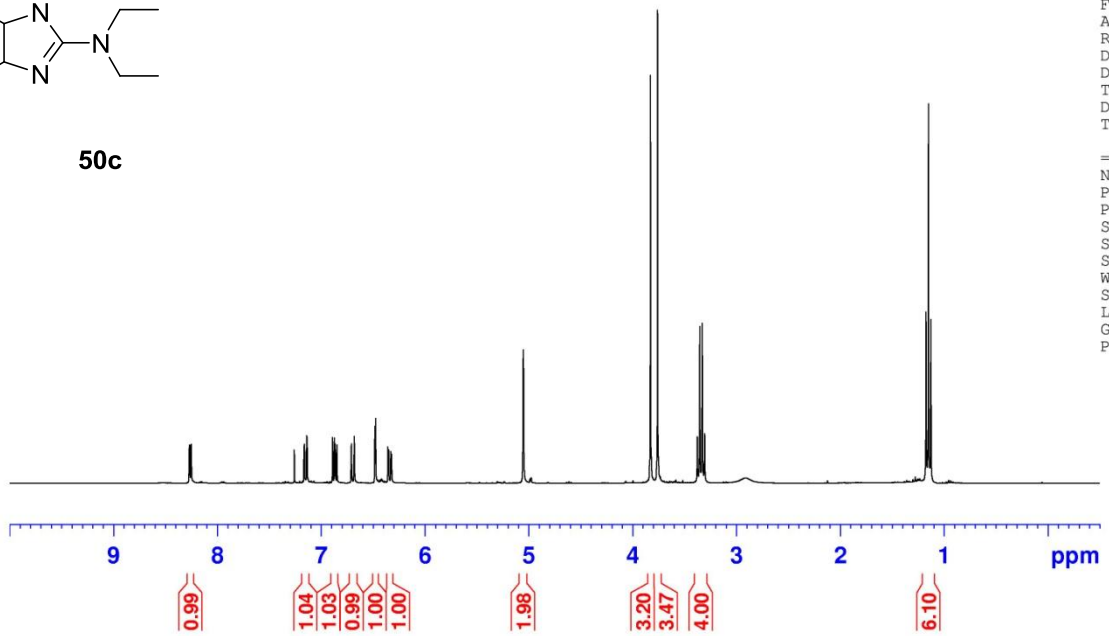
50b

AJR-5-058
Post Column



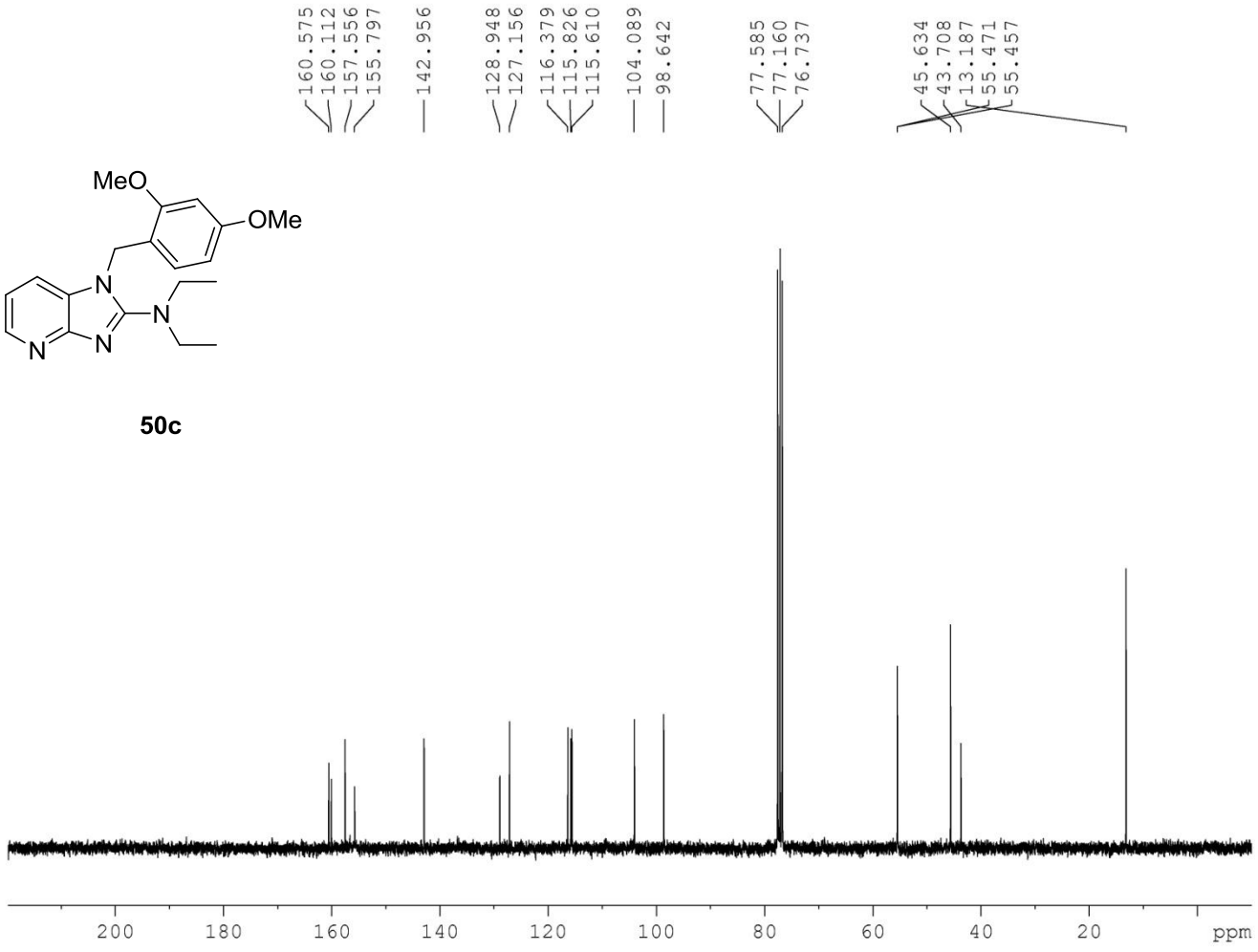


50c



NAME	AJR-5-058
EXPNO	3
PROCNO	1
Date_	20120801
Time	12.01
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	71.8
DW	139.200 usec
DE	54.00 usec
TE	295.2 K
D1	5.00000000 sec
TD0	1

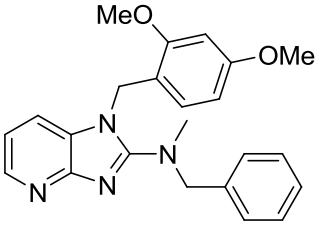
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300062 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00


160.575
160.112
157.556
155.797
142.956
128.948
127.156
116.379
115.826
115.610
104.089
98.642
77.585
77.160
76.737
45.634
43.708
13.187
55.471
55.457
MeO
OMe
N
N
N
N
200
180
160
140
120
100
80
60
40
20
ppm

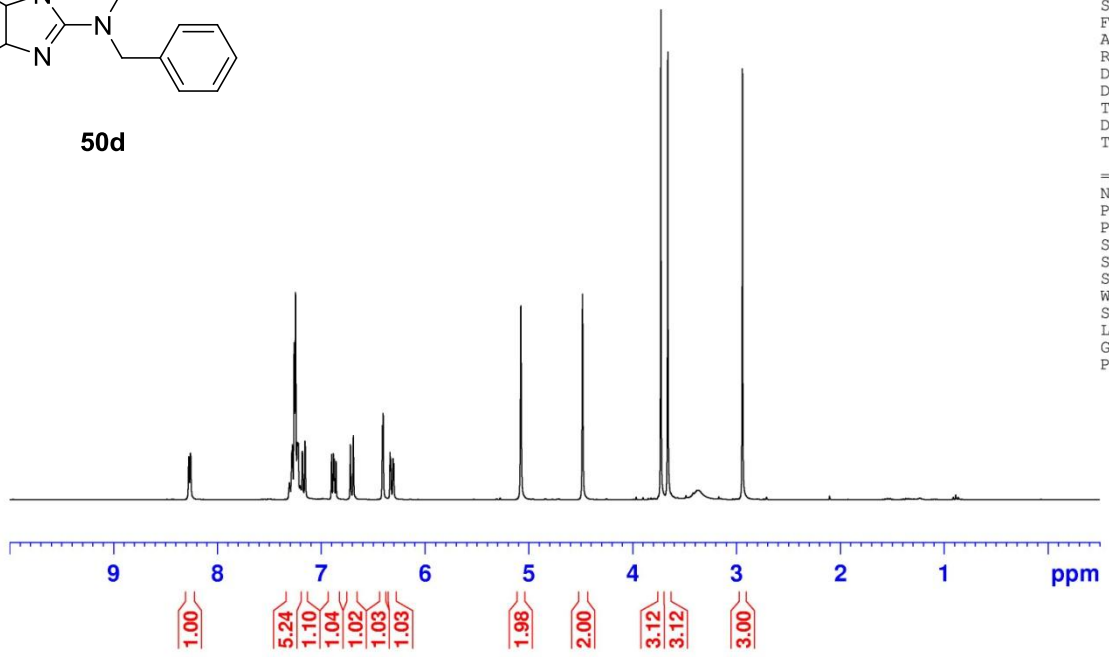
50c

AJR-5-034

8.258
7.309
7.286
7.280
7.262
7.249
7.233
7.226
7.223
7.184
7.180
7.158
7.154
6.901
6.885
6.875
6.859
6.720
6.692
6.412
6.404
6.338
6.330
6.310
6.302
5.078
4.484
3.729
3.663
2.943



50d

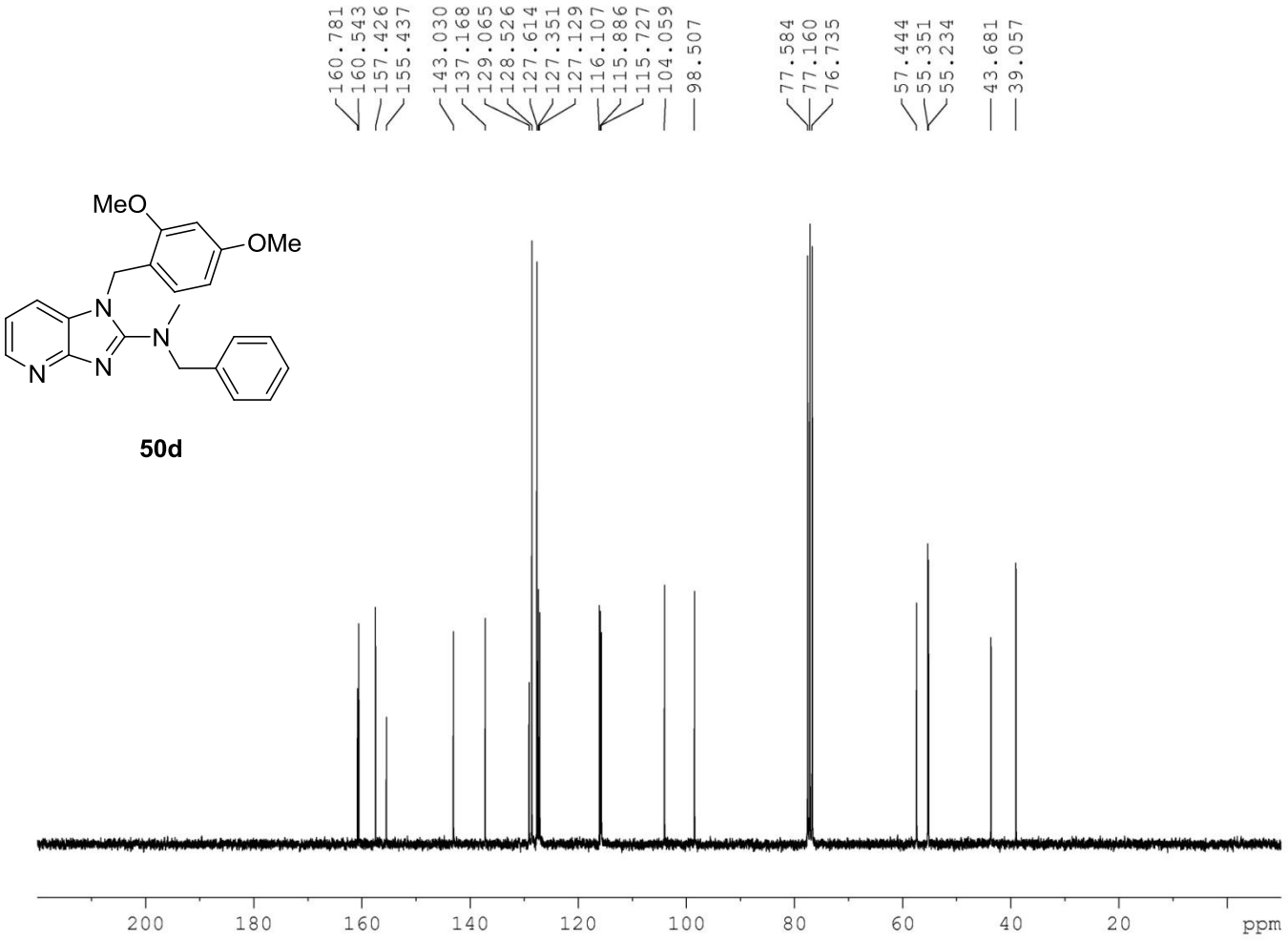


BRUKER

NAME	AJR-5-034
EXPNO	3
PROCNO	1
Date_	20120702
Time	18.02
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	28.5
DW	139.200 usec
DE	54.00 usec
TE	295.2 K
D1	5.00000000 sec
TD0	1

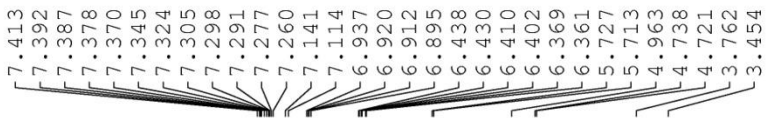
======== CHANNEL f1 ========

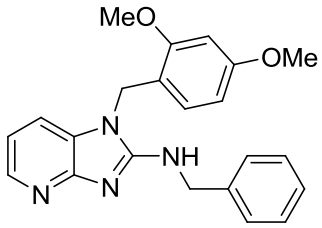
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300060 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00


160.781
160.543
157.426
155.437
143.030
137.168
129.065
128.526
127.614
127.351
127.129
116.107
115.886
115.727
104.059
98.507
77.584
77.160
76.735
57.444
55.351
55.234
43.681
39.057
MeO
OMe
N
N
N
N
200
180
160
140
120
100
80
60
40
20
ppm

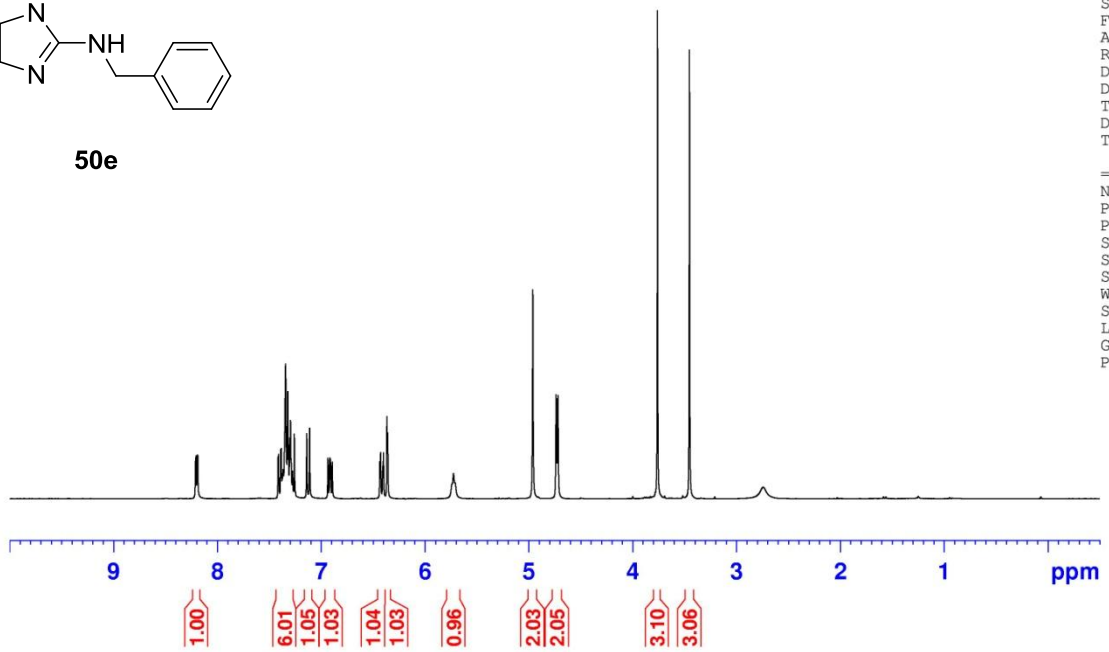
50d

AJ-1-45
after column (final b)

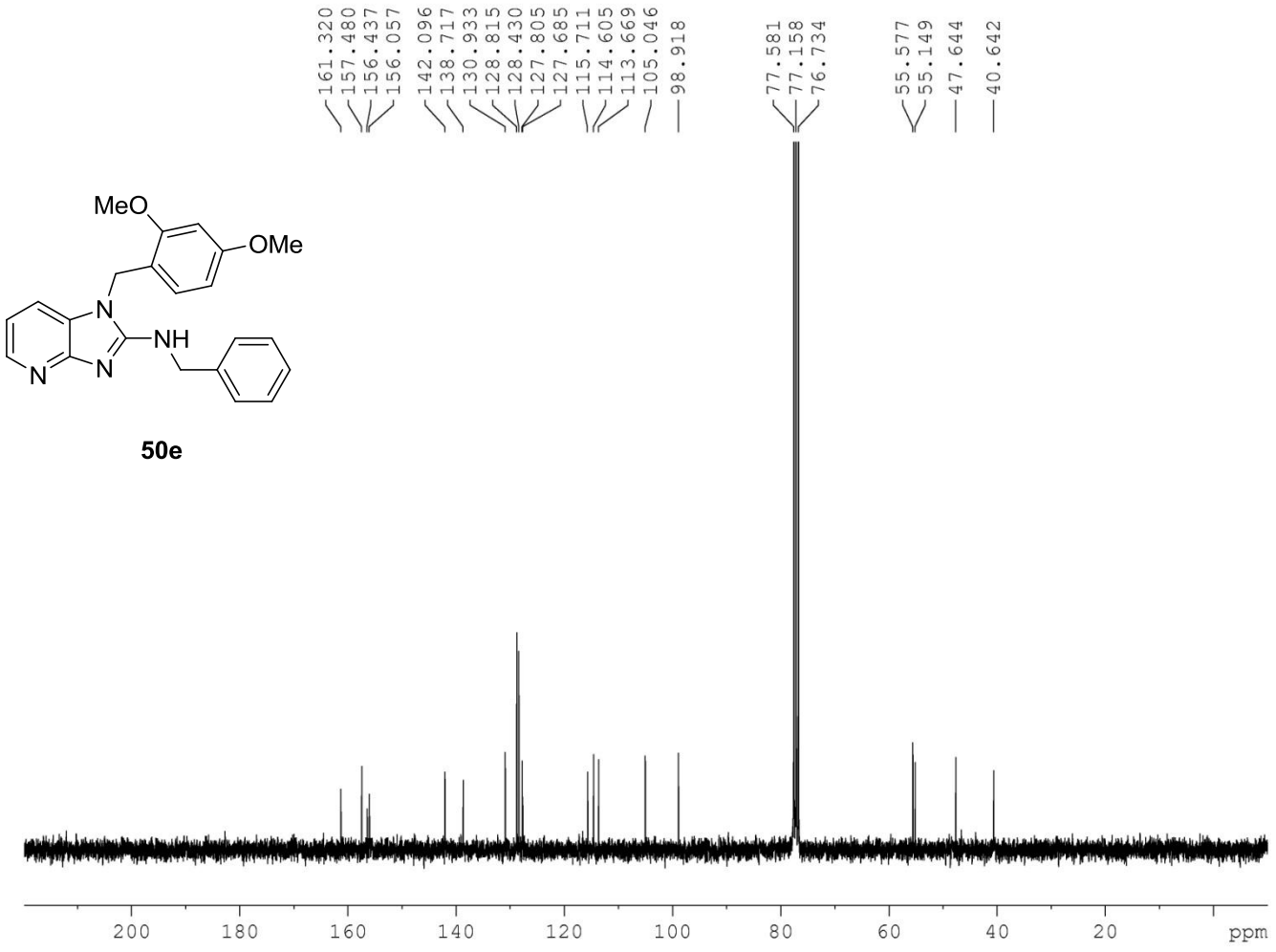




50e



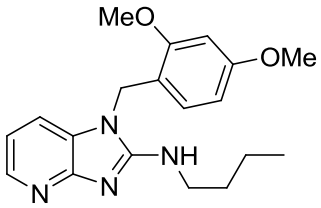
NAME	AJ-1-45	
EXPNO	6	
PROCNO	1	
Date_	20120806	
Time	12.45	
INSTRUM	spect	
PROBHD	5 mm QNP 1H/1	
PULPROG	zg	
TD	32768	
SOLVENT	CDCl3	
NS	12	
DS	0	
SWH	3591.954	Hz
FIDRES	0.109618	Hz
AQ	4.5613556	sec
RG	1290.2	
DW	139.200	usec
DE	54.00	usec
TE	295.2	K
D1	5.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	9.75	usec
PL1	0.00	dB
SFO1	300.1315007	MHz
SI	32768	
SF	300.1300062	MHz
WDW	EM	
SSB	0	
LB	0.20	Hz
GB	0	
PC	1.00	


161.320
157.480
156.437
156.057
142.096
138.717
130.933
128.815
128.430
127.805
127.685
115.711
114.605
113.669
105.046
98.918
77.581
77.158
76.734
55.577
55.149
47.644
40.642
MeO
OMe
N
NH
N
N
200
180
160
140
120
100
80
60
40
20
ppm

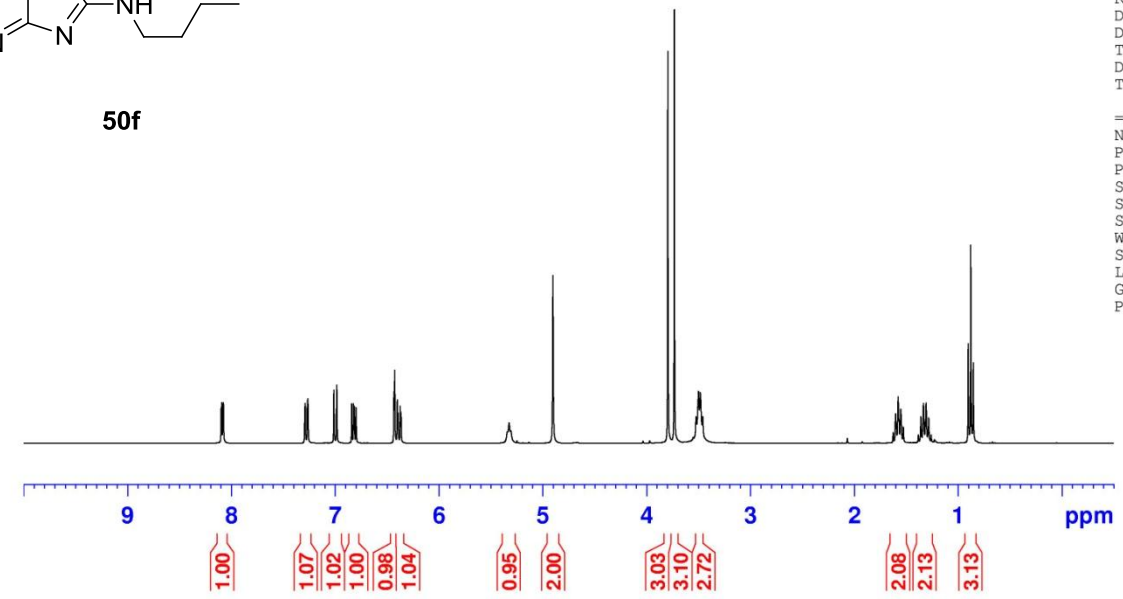
50e

AJR-5-057
Post Column

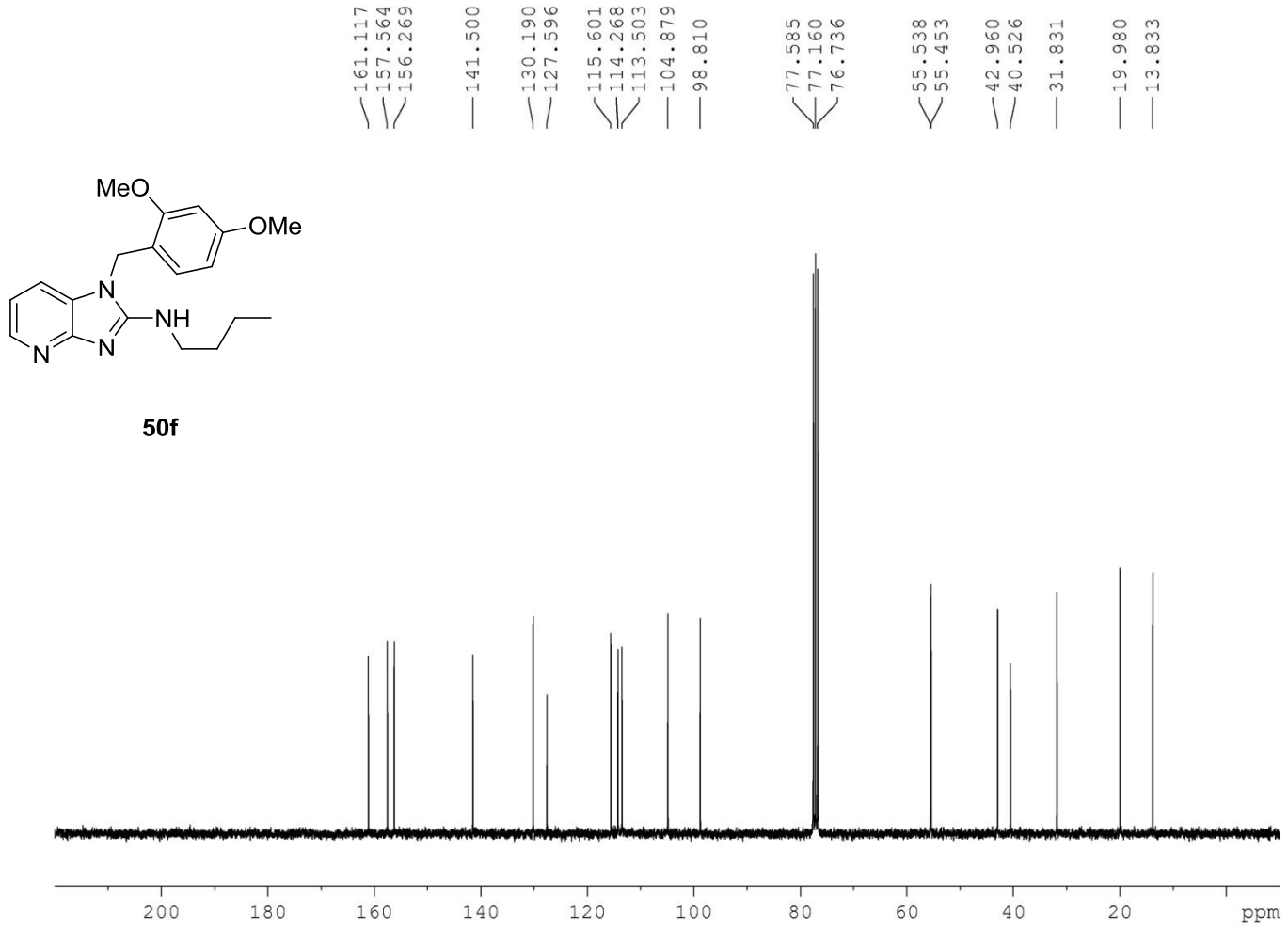
8.100 8.096 8.083 8.079 7.295 7.291 7.270 7.265 7.015 6.987 6.843 6.826 6.817 6.800 6.436 6.428 6.403 6.396 6.376 6.368 5.343 5.327 5.310 4.904 3.797 3.735 3.525 3.502 3.484 3.461 1.626 1.602 1.595 1.578 1.570 1.554 1.528 1.359 1.333 1.308 1.284 0.903 0.879 0.854



50f



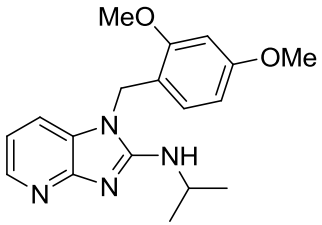
NAME	AJR-5-057
EXPNO	1
PROCNO	1
Date_	20120727
Time	9.26
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	40.3
DW	139.200 usec
DE	54.00 usec
TE	295.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300060 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00


161.117
157.564
156.269
141.500
130.190
127.596
115.601
114.268
113.503
104.879
98.810
77.585
77.160
76.736
55.538
55.453
42.960
40.526
31.831
19.980
13.833
MeO
OMe
N
NH
N
N
200
180
160
140
120
100
80
60
40
20
ppm

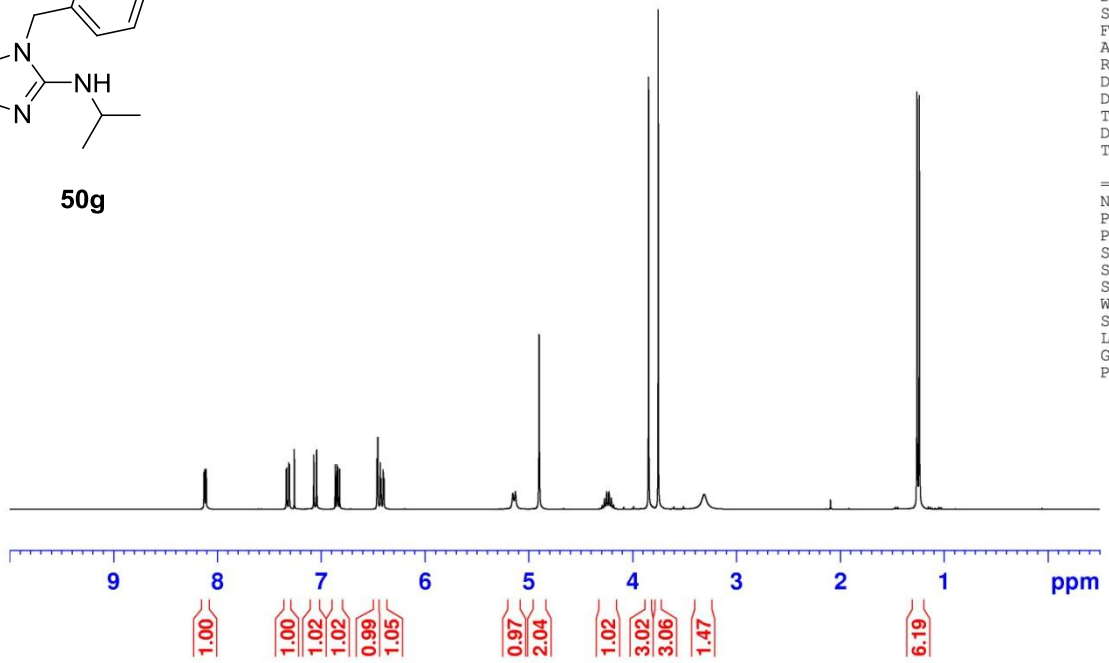
50f

AJR-5-052
Post Column

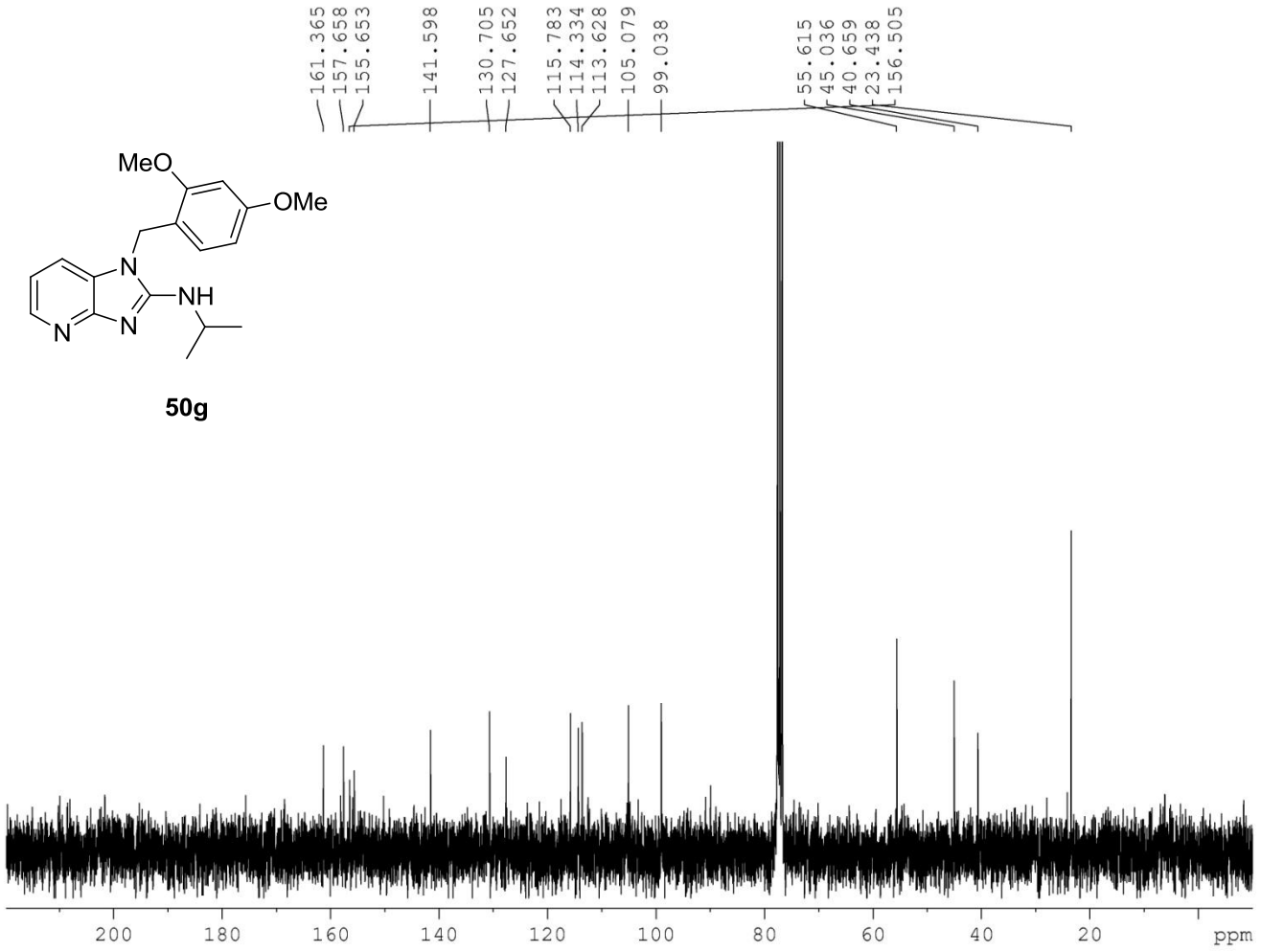
8.126 8.114 8.109 7.339 7.334 7.313 7.308 7.260 7.073 7.045 6.867 6.850 6.841 6.824 6.464 6.456 6.432 6.424 6.404 6.396 5.156 5.131 4.902 4.316 4.295 4.273 4.251 4.228 4.206 4.184 4.163 3.847 3.755 1.261 1.239



50g



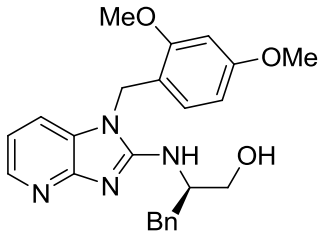
NAME	AJR-5-052	
EXPNO	3	
PROCNO	1	
Date_	20120801	
Time	17.24	
INSTRUM	spect	
PROBHD	5 mm QNP 1H/1	
PULPROG	zg	
TD	32768	
SOLVENT	CDCl3	
NS	16	
DS	0	
SWH	3591.954	Hz
FIDRES	0.109618	Hz
AQ	4.5613556	sec
RG	90.5	
DW	139.200	usec
DE	54.00	usec
TE	296.2	K
D1	5.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	9.75	usec
PL1	0.00	dB
SFO1	300.1315007	MHz
SI	32768	
SF	300.1300062	MHz
WDW	EM	
SSB	0	
LB	0.20	Hz
GB	0	
PC	1.00	


161.365
157.658
155.653
141.598
130.705
127.652
115.783
114.334
113.628
105.079
99.038
55.615
45.036
40.659
23.438
156.505
MeO
OMe
N
NH
N
N
200
180
160
140
120
100
80
60
40
20
ppm

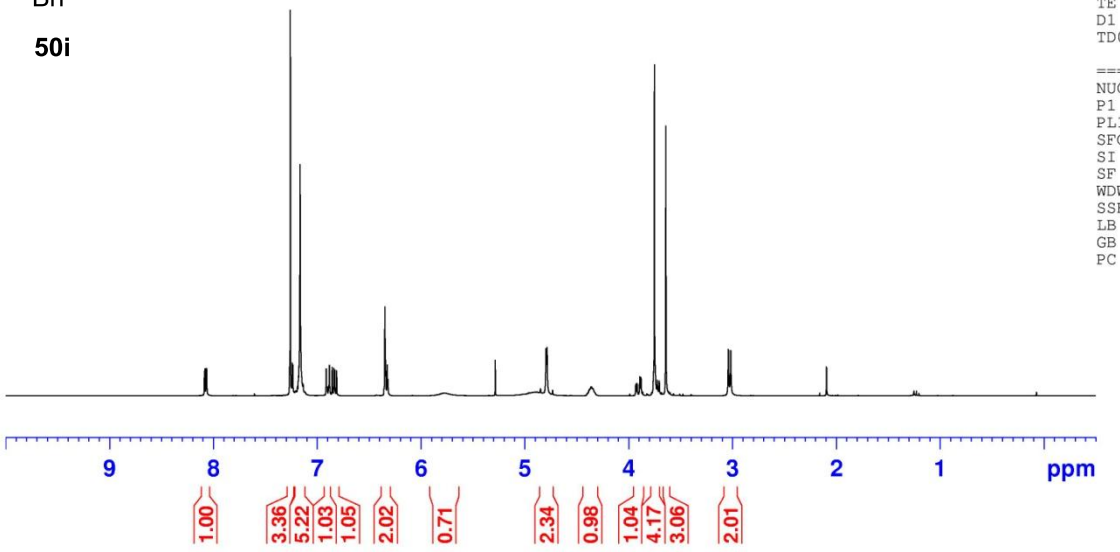
50g

AJR-5-053
Post Column

8.083 8.071 8.066 7.268 7.260 7.242 7.237 7.177 7.167 6.914 6.884 6.857 6.840 6.832 6.815 6.349 6.342 6.327 6.319 4.851 4.797 4.788 4.733 4.376 4.360 4.347 3.932 3.920 3.894 3.882 3.760 3.753 3.745 3.724 3.706 3.643 3.041 3.018

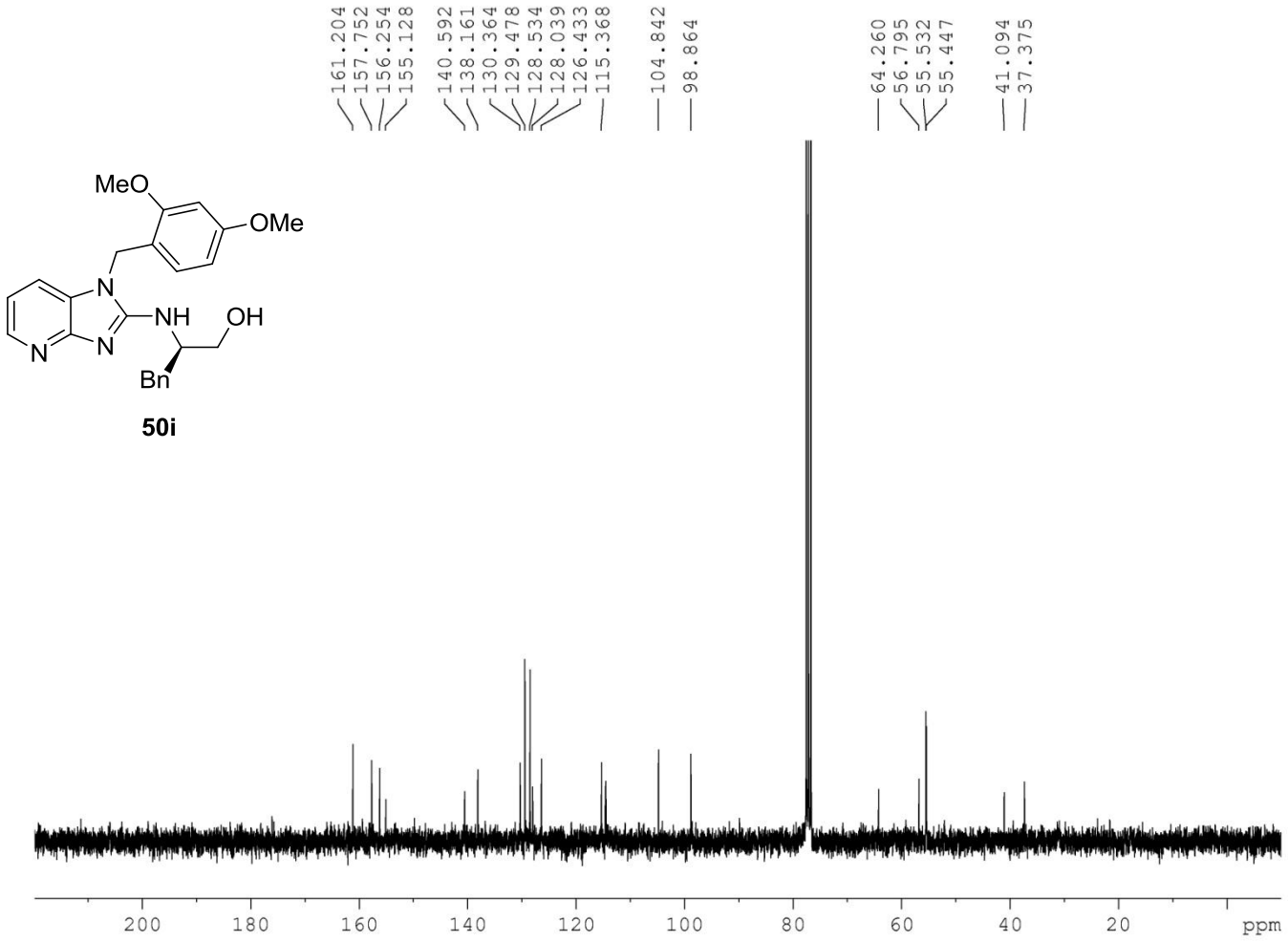


50i

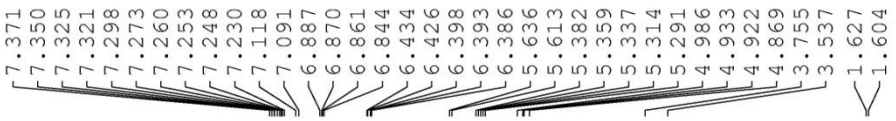


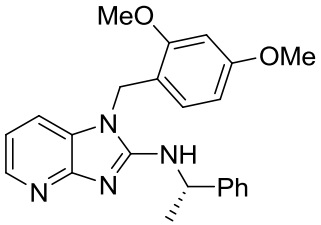
BRUKER

NAME	AJR-5-053	
EXPNO	3	
PROCNO	1	
Date_	20120801	
Time	17.32	
INSTRUM	spect	
PROBHD	5 mm QNP 1H/1	
PULPROG	zg	
TD	32768	
SOLVENT	CDCl3	
NS	16	
DS	0	
SWH	3591.954	Hz
FIDRES	0.109618	Hz
AQ	4.5613556	sec
RG	114	
DW	139.200	usec
DE	54.00	usec
TE	301.2	K
D1	5.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	9.75	usec
PL1	0.00	dB
SFO1	300.1315007	MHz
SI	32768	
SF	300.1300062	MHz
WDW	EM	
SSB	0	
LB	0.20	Hz
GB	0	
PC	1.00	

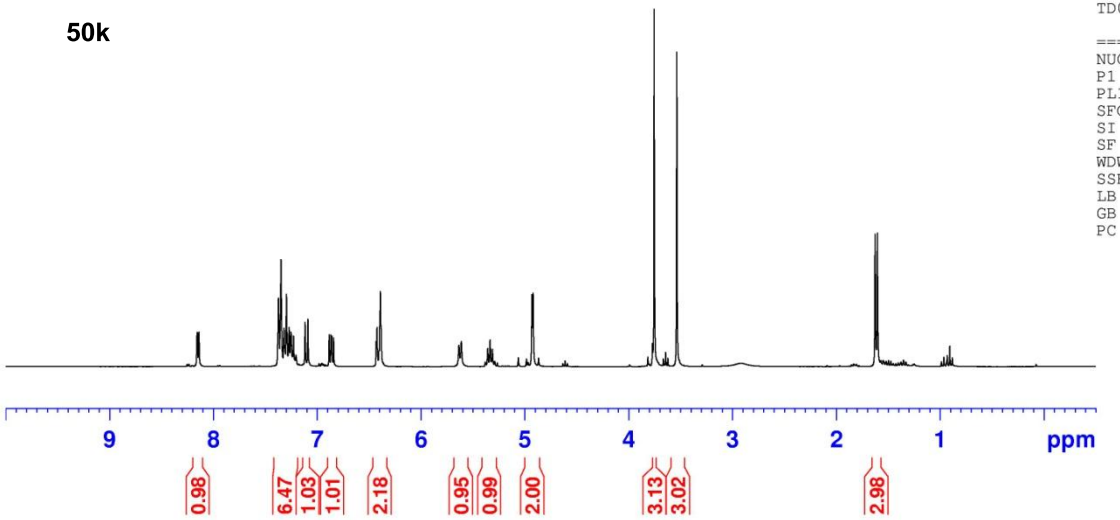

161.204
157.752
156.254
155.128
140.592
138.161
130.364
129.478
128.534
128.039
126.433
115.368
104.842
98.864
64.260
56.795
55.532
55.447
41.094
37.375
MeO
OMe
N
NH
OH
N
N
Bn
50i
200
180
160
140
120
100
80
60
40
20
ppm

AJR-5-074
Post Column



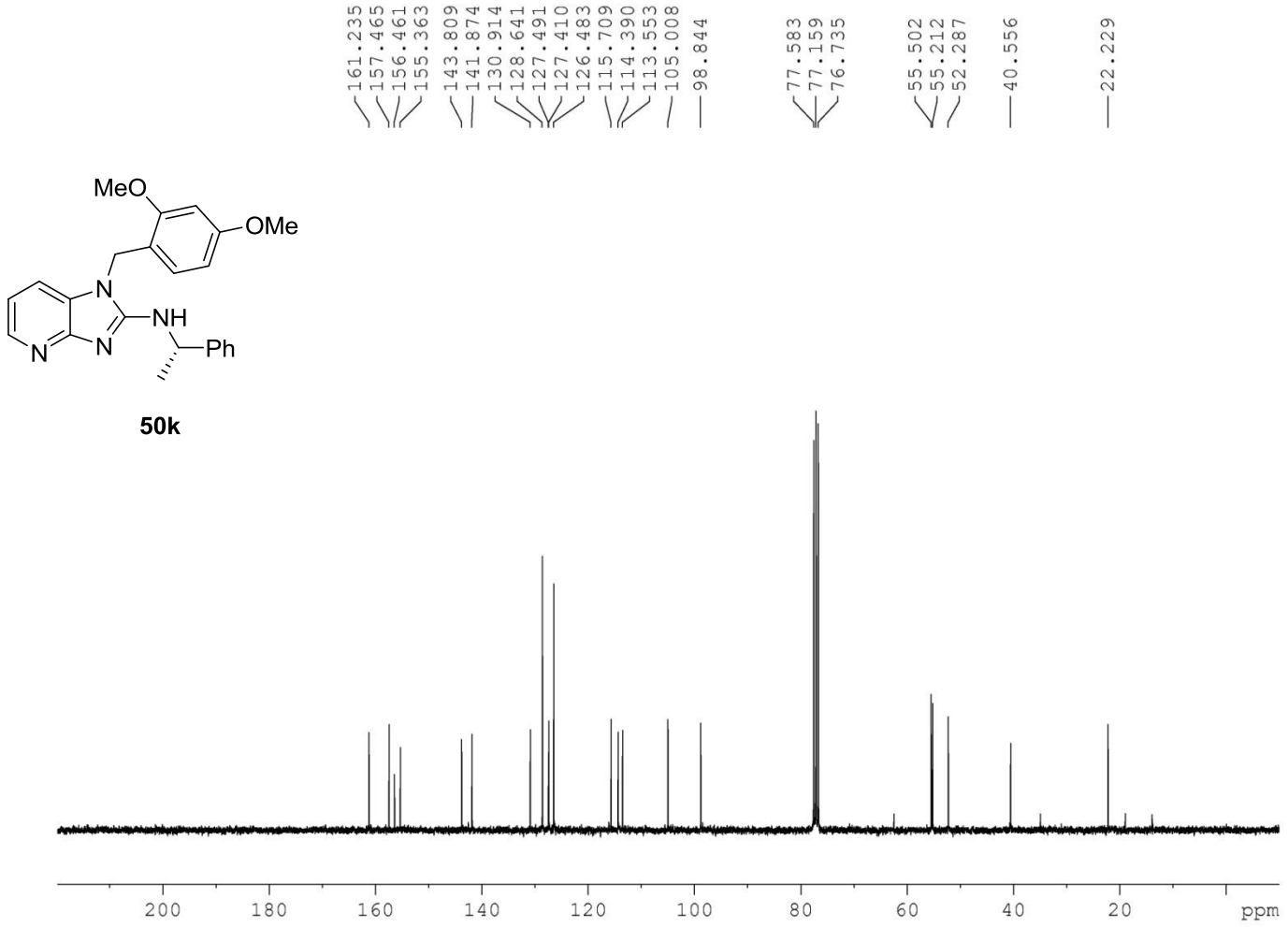


50k



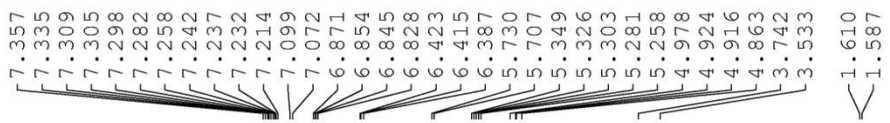
BRUKER

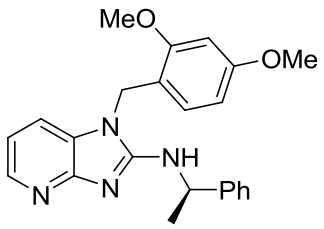
NAME	AJR-5-074	
EXPNO	2	
PROCNO	1	
Date_	20120808	
Time	10.02	
INSTRUM	spect	
PROBHD	5 mm QNP 1H/1	
PULPROG	zg	
TD	32768	
SOLVENT	CDCl3	
NS	16	
DS	0	
SWH	3591.954	Hz
FIDRES	0.109618	Hz
AQ	4.5613556	sec
RG	57	
DW	139.200	usec
DE	54.00	usec
TE	294.2	K
D1	5.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	9.75	usec
PL1	0.00	dB
SFO1	300.1315007	MHz
SI	32768	
SF	300.1300061	MHz
WDW	EM	
SSB	0	
LB	0.20	Hz
GB	0	
PC	1.00	


161.235
157.465
156.461
155.363
143.809
141.874
130.914
128.641
127.491
127.410
126.483
115.709
114.390
113.553
105.008
98.844
77.583
77.159
76.735
55.502
55.212
52.287
40.556
22.229
MeO
OMe
N
NH
N
N
Ph
200
180
160
140
120
100
80
60
40
20
ppm

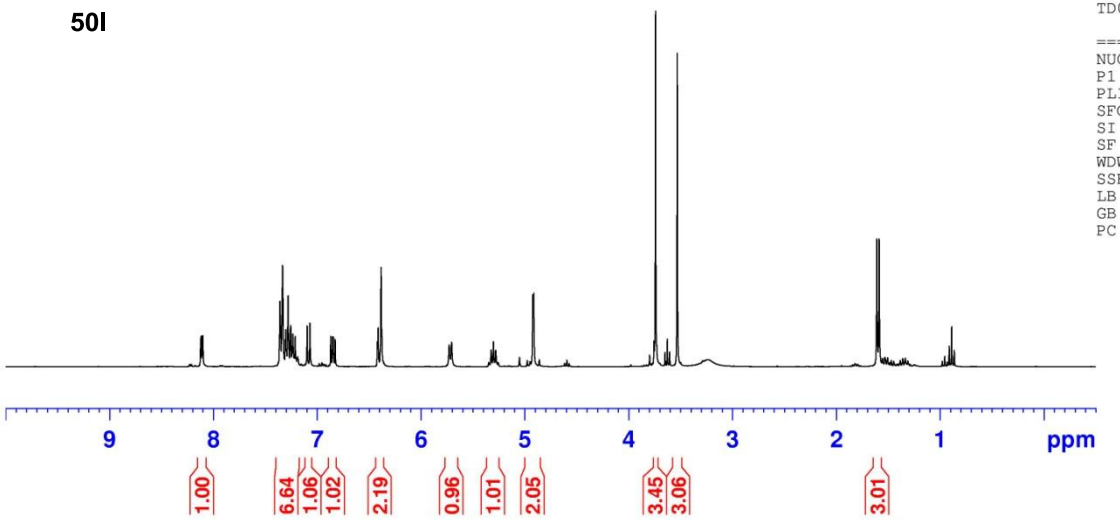
50k

AJR-5-075
Post Column

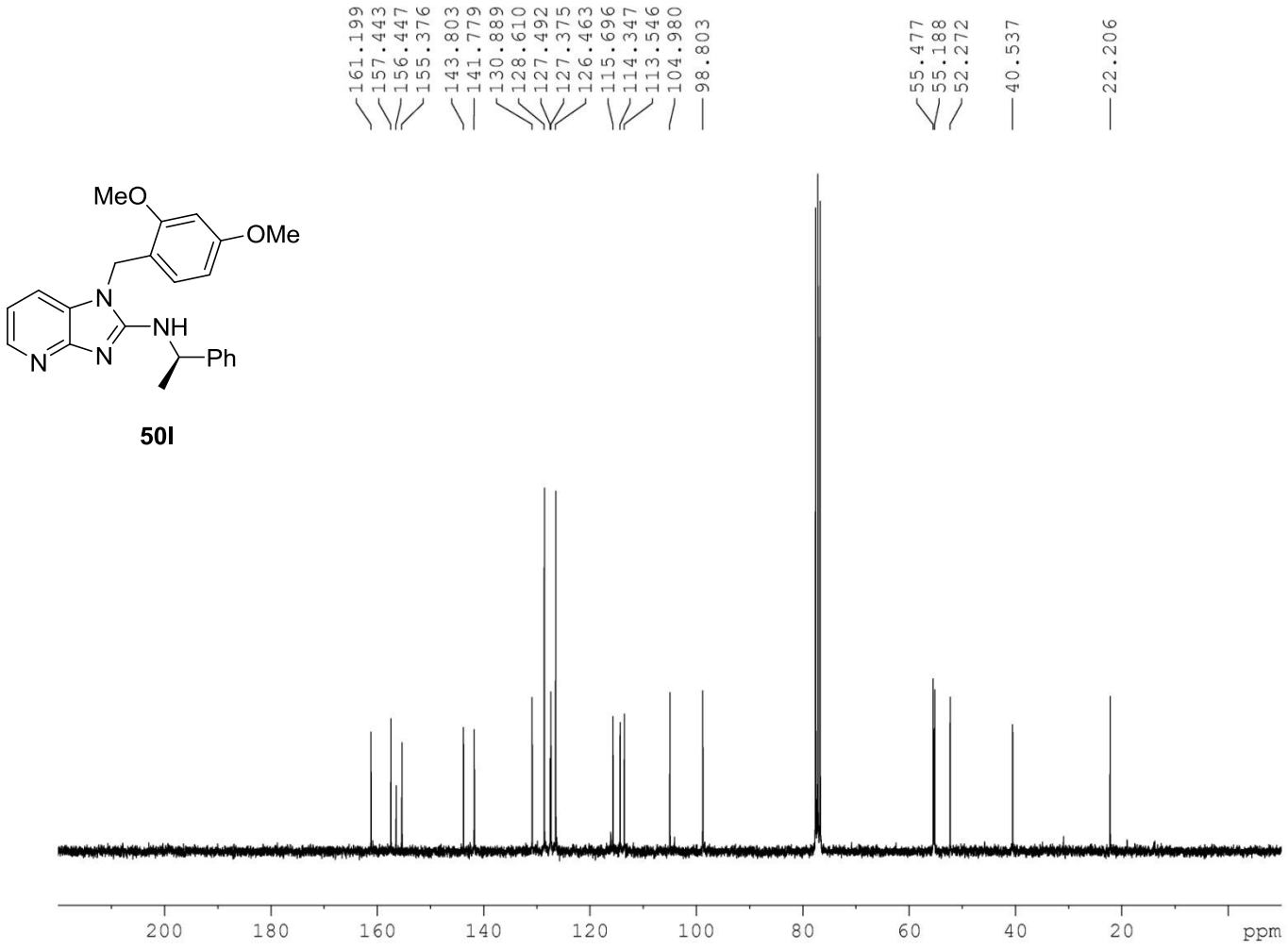




50l

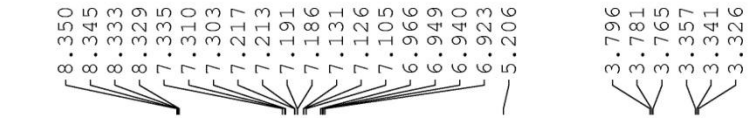


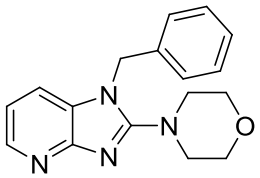
NAME	AJR-5-075	
EXPNO	2	
PROCNO	1	
Date_	20120813	
Time	8.47	
INSTRUM	spect	
PROBHD	5 mm QNP 1H/1	
PULPROG	zg	
TD	32768	
SOLVENT	CDCl3	
NS	16	
DS	0	
SWH	3591.954	Hz
FIDRES	0.109618	Hz
AQ	4.5613556	sec
RG	40.3	
DW	139.200	usec
DE	54.00	usec
TE	294.2	K
D1	5.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	9.75	usec
PL1	0.00	dB
SFO1	300.1315007	MHz
SI	32768	
SF	300.1300061	MHz
WDW	EM	
SSB	0	
LB	0.20	Hz
GB	0	
PC	1.00	


161.199
157.443
156.447
155.376
143.803
141.779
130.889
128.610
127.492
127.375
126.463
115.696
114.347
113.546
104.980
98.803
55.477
55.188
52.272
40.537
22.206
MeO
OMe
N
NH
N
N
Ph
200
180
160
140
120
100
80
60
40
20
ppm

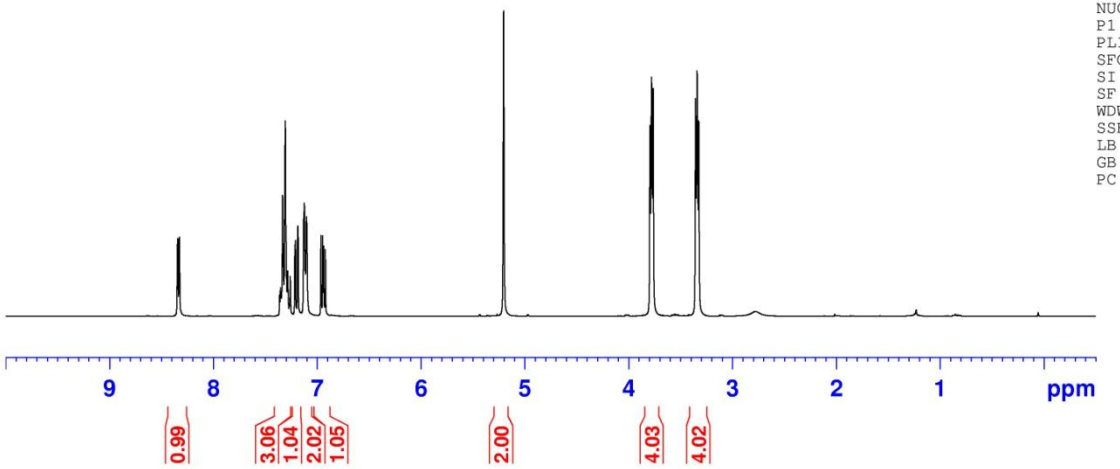
50l

AJ-1-56
after column

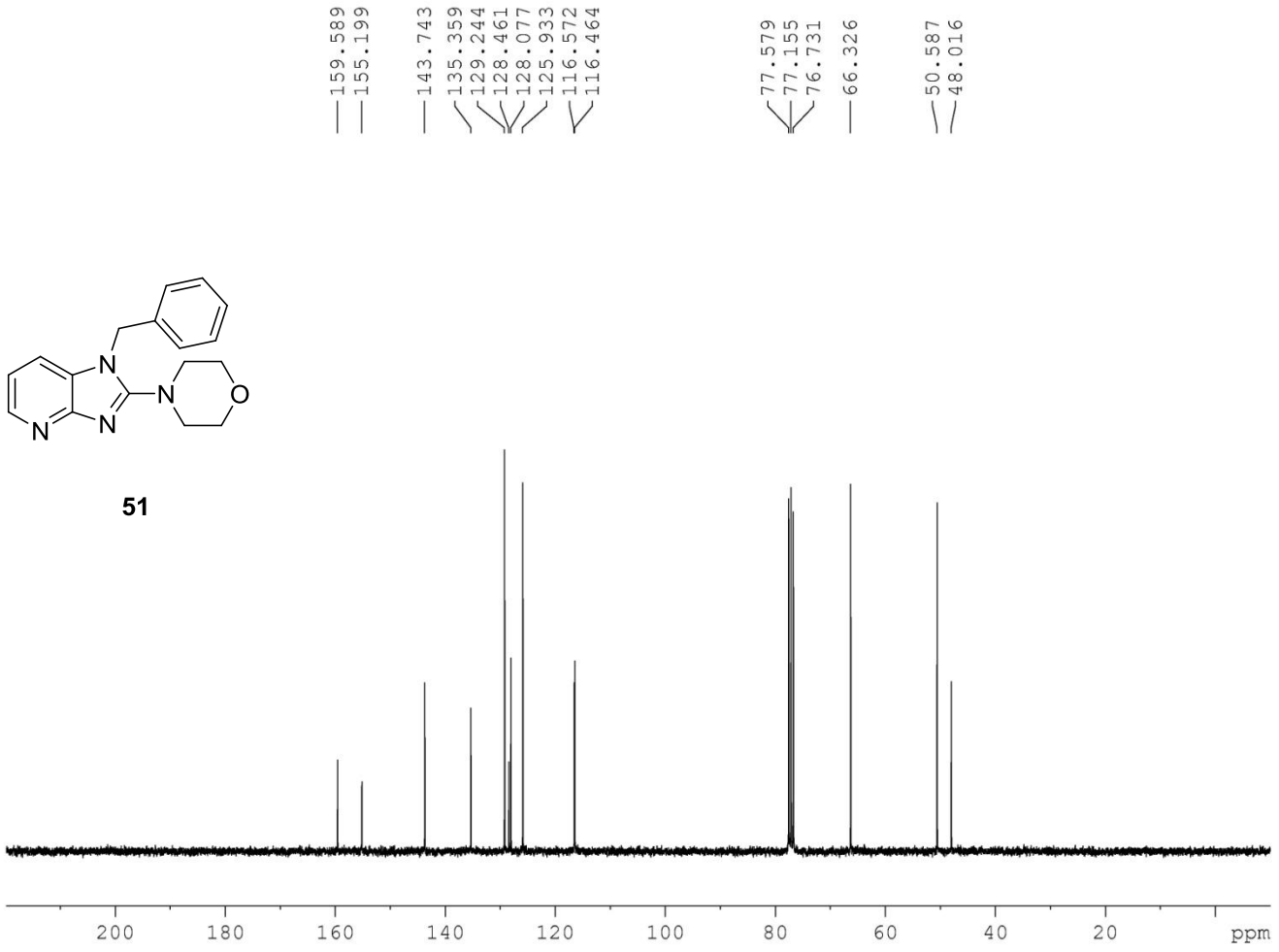




51

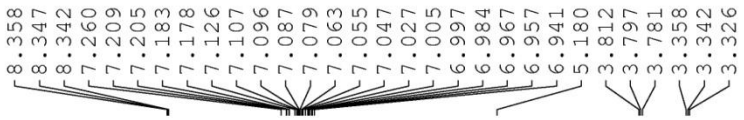


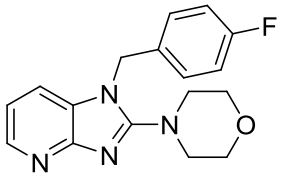
NAME	AJ-1-56
EXPNO	3
PROCNO	1
Date_	20120710
Time	18.51
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	80.6
DW	139.200 usec
DE	54.00 usec
TE	294.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300061 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00


159.589
155.199
143.743
135.359
129.244
128.461
128.077
125.933
116.572
116.464
77.579
77.155
76.731
66.326
50.587
48.016
N
N
N
N
O
200
180
160
140
120
100
80
60
40
20
ppm

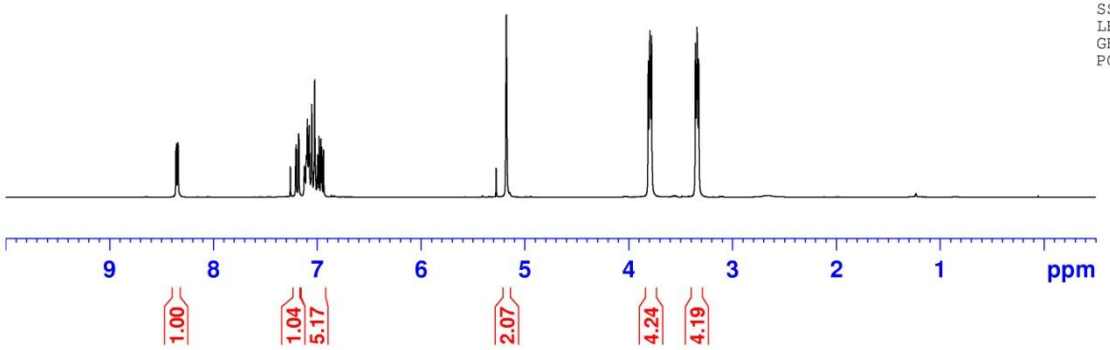
51

TW-1-61
after column



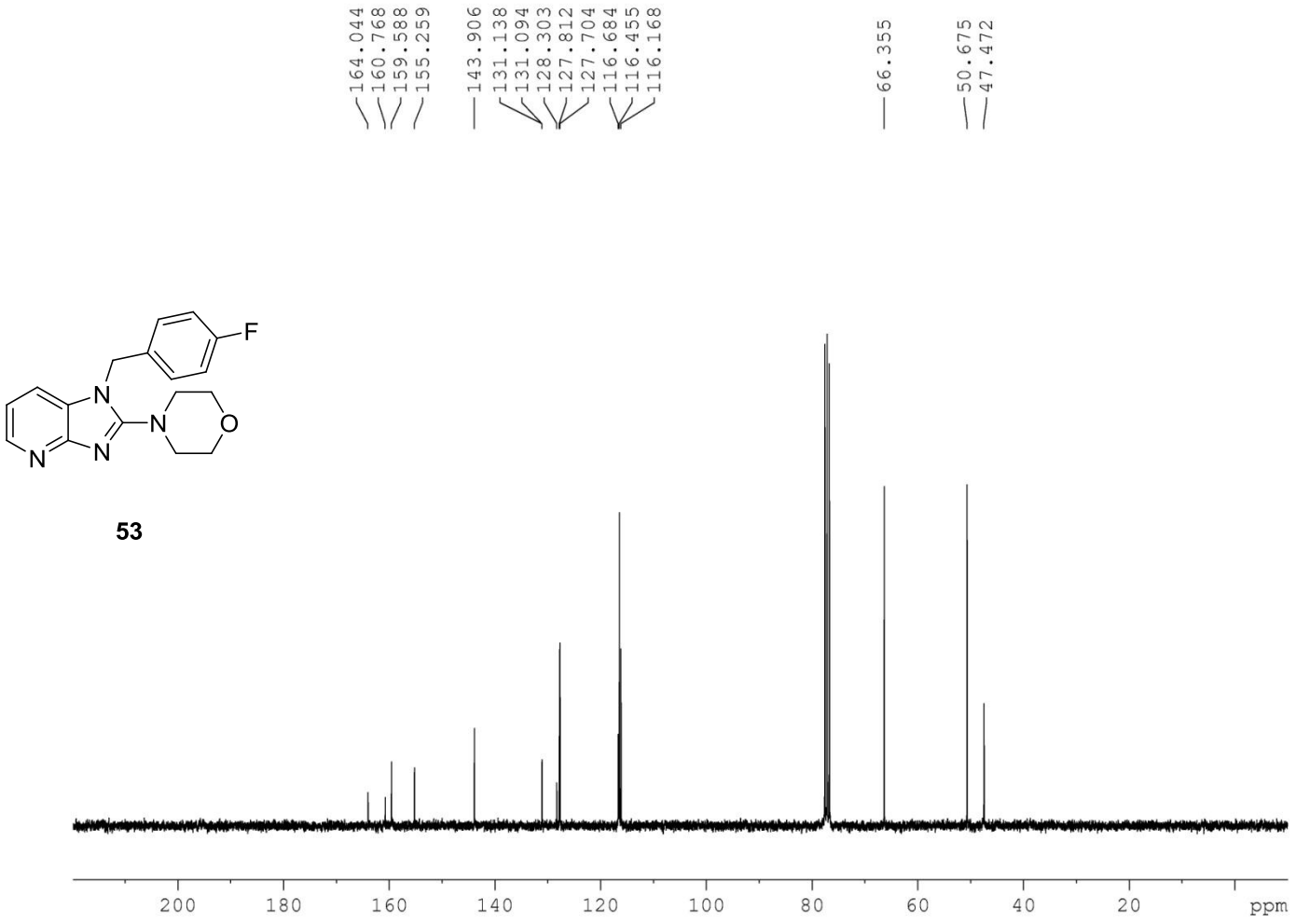


53

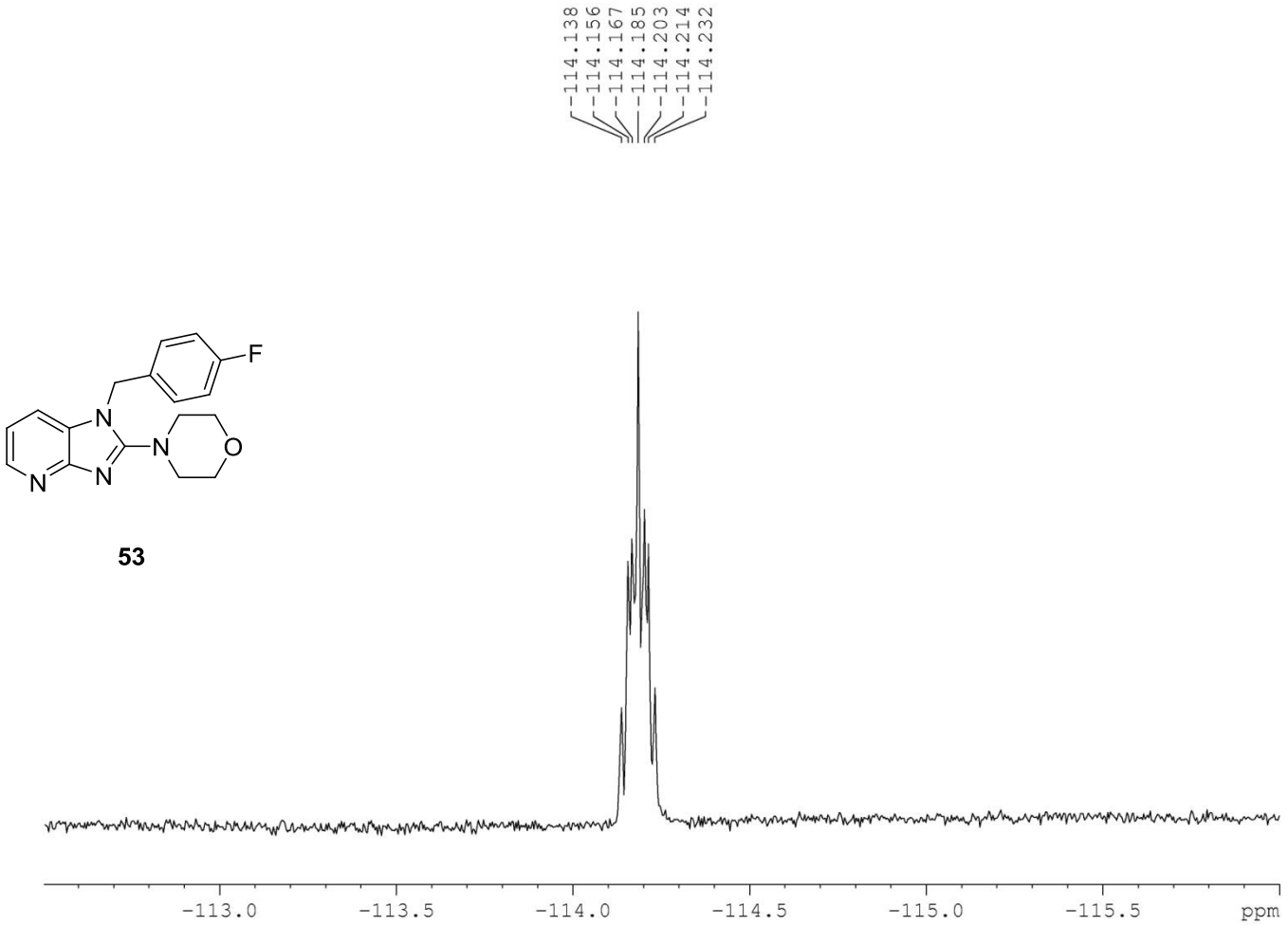


BRUKER

NAME	Tw-1-61	
EXPNO	2	
PROCNO	1	
Date_	20120717	
Time	14.34	
INSTRUM	spect	
PROBHD	5 mm QNP 1H/1	
PULPROG	zg	
TD	32768	
SOLVENT	CDCl3	
NS	16	
DS	0	
SWH	3591.954	Hz
FIDRES	0.109618	Hz
AQ	4.5613556	sec
RG	143.7	
DW	139.200	usec
DE	54.00	usec
TE	295.2	K
D1	3.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	9.75	usec
PL1	0.00	dB
SFO1	300.1315007	MHz
SI	32768	
SF	300.1300062	MHz
WDW	EM	
SSB	0	
LB	0.20	Hz
GB	0	
PC	1.00	

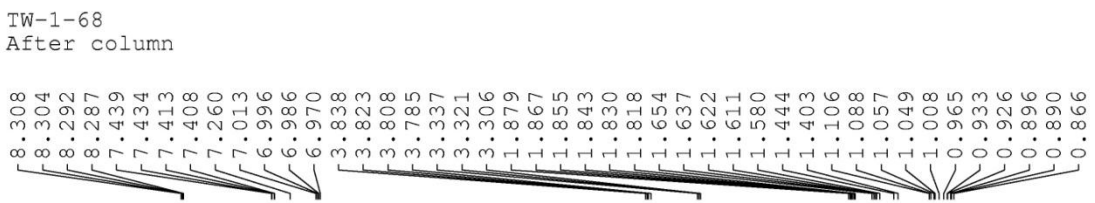

164.044
160.768
159.588
155.259
143.906
131.138
131.094
128.303
127.812
127.704
116.684
116.455
116.168
66.355
50.675
47.472
F
N
N
N
N
O
200
180
160
140
120
100
80
60
40
20
ppm

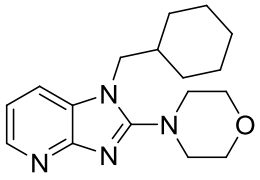
53


-114.138
-114.156
-114.167
-114.185
-114.203
-114.214
-114.232
F
N
N
N
N
O
-113.0
-113.5
-114.0
-114.5
-115.0
-115.5
ppm

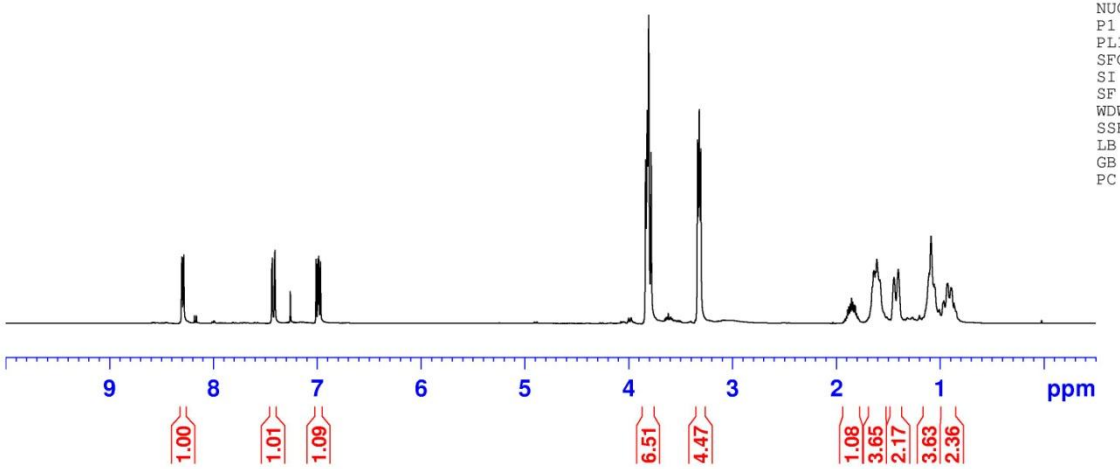
53

TW-1-68
After column

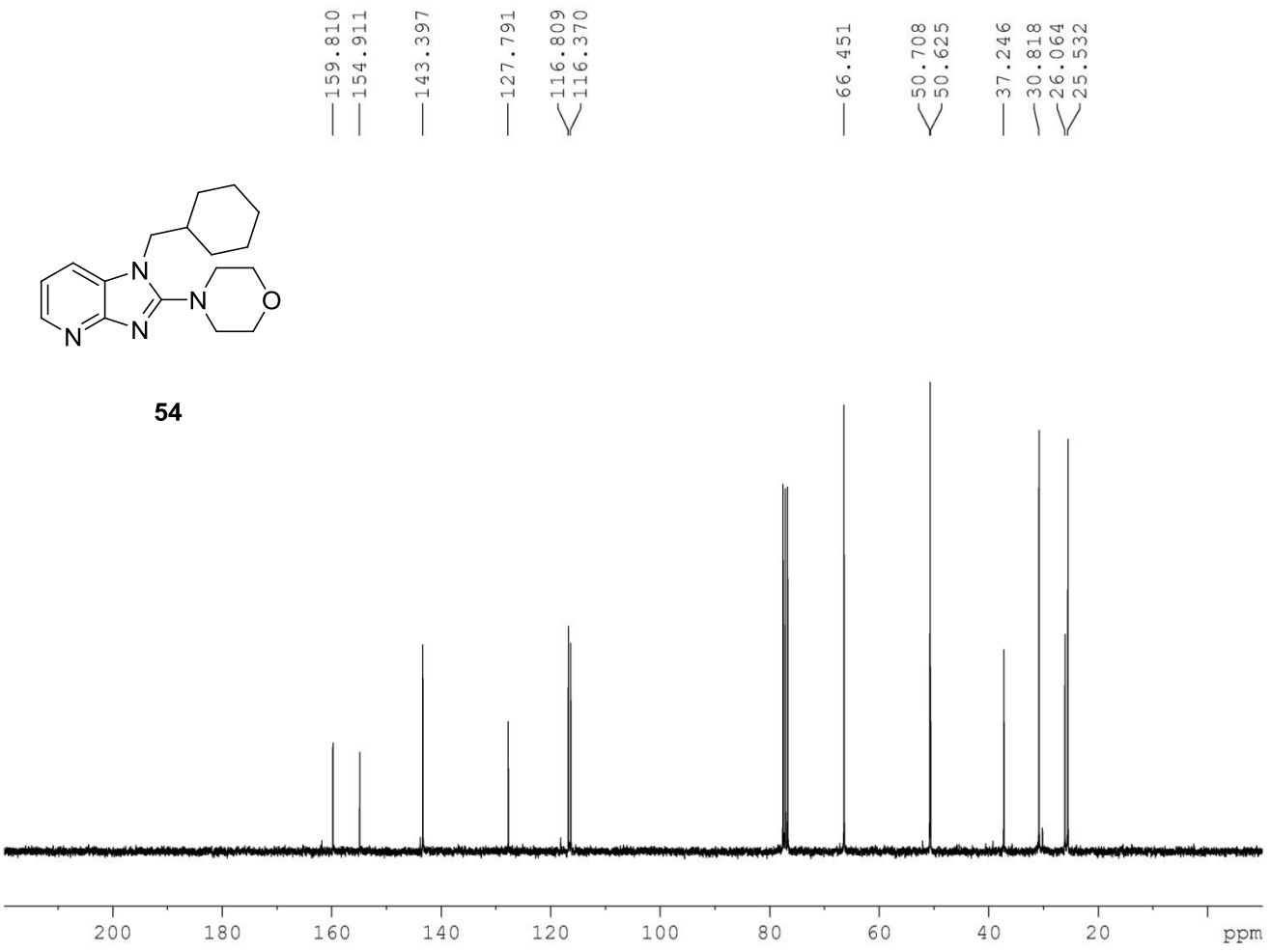




54

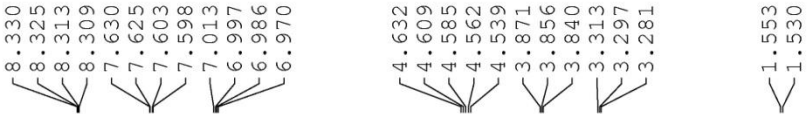


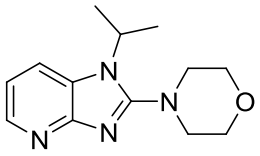
NAME	Tw-1-68	
EXPNO	4	
PROCNO	1	
Date_	20120802	
Time	9.34	
INSTRUM	spect	
PROBHD	5 mm QNP 1H/1	
PULPROG	zg	
TD	32768	
SOLVENT	CDCl3	
NS	16	
DS	0	
SWH	3591.954	Hz
FIDRES	0.109618	Hz
AQ	4.5613556	sec
RG	35.9	
DW	139.200	usec
DE	54.00	usec
TE	310.2	K
D1	3.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	9.75	usec
PL1	0.00	dB
SFO1	300.1315007	MHz
SI	32768	
SF	300.1300062	MHz
WDW	EM	
SSB	0	
LB	0.20	Hz
GB	0	
PC	1.00	


159.810
154.911
143.397
127.791
116.809
116.370
66.451
50.708
50.625
37.246
30.818
26.064
25.532
N
N
N
N
O
200
180
160
140
120
100
80
60
40
20
ppm

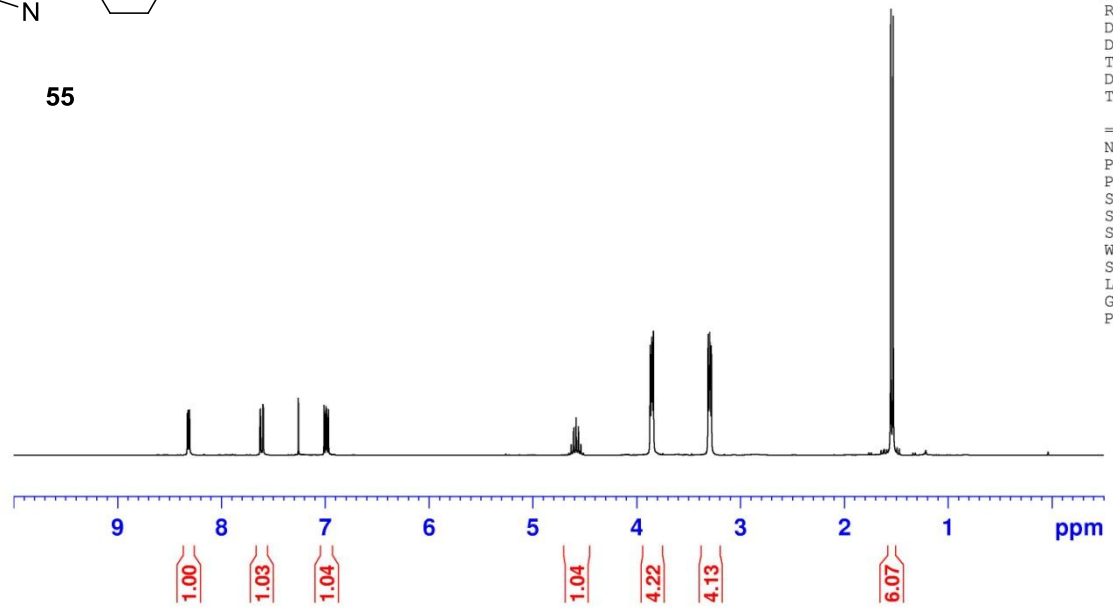
54

AJ-1-67
after column

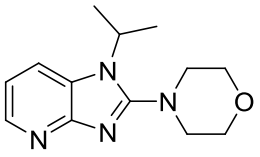




55



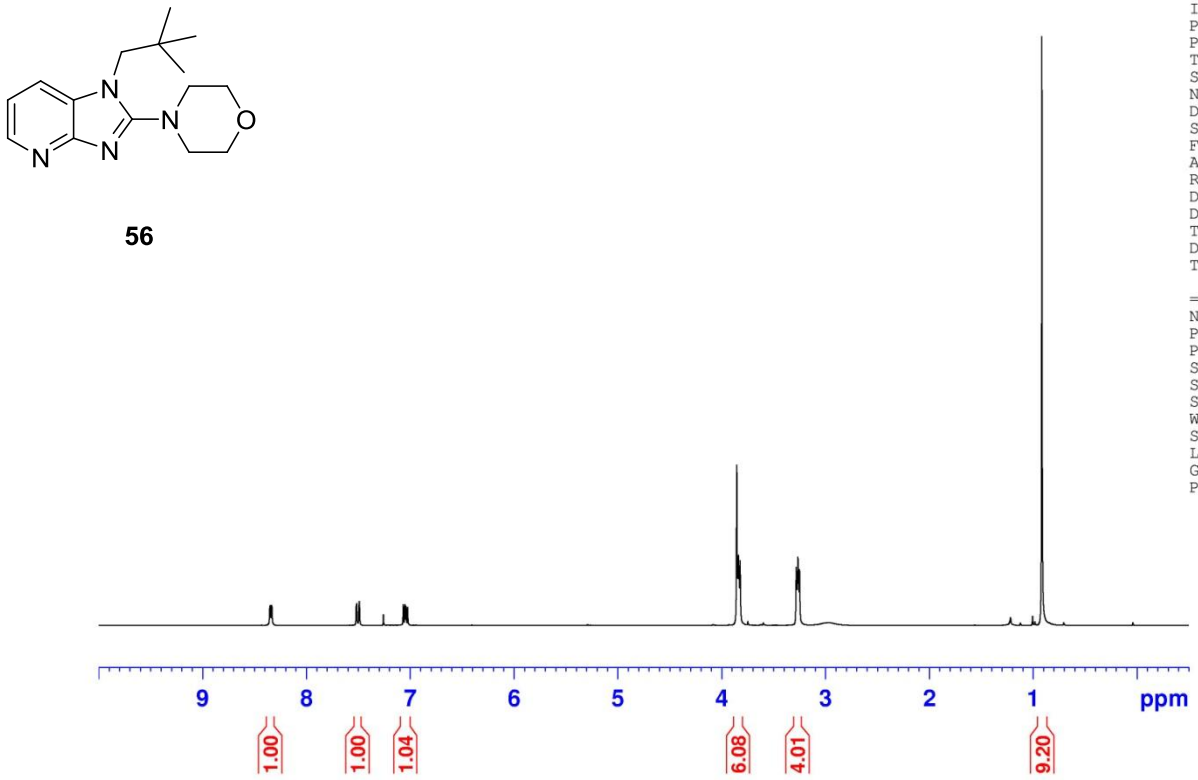
NAME	AJ-1-67
EXPNO	2
PROCNO	1
Date_	20120731
Time	11.42
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	12
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	28.5
DW	139.200 usec
DE	54.00 usec
TE	295.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300063 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00



55

159.227
155.477
143.285
125.636
118.446
116.164
77.591
77.166
76.743
66.419
51.368
47.974
21.312
200
180
160
140
120
100
80
60
40
20
ppm

AJ-1-62
after column (final)

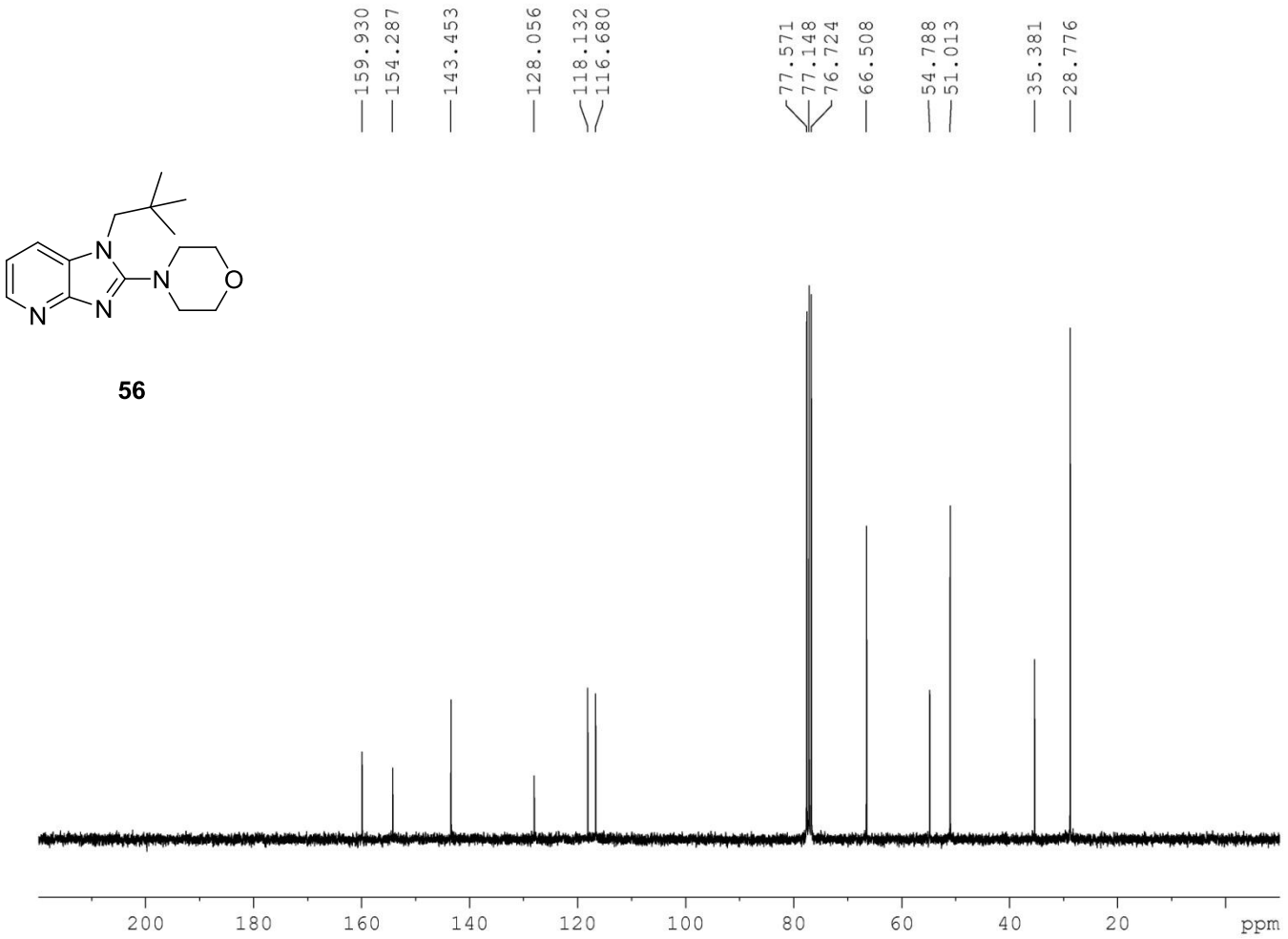


56

NAME	AJ-1-62
EXPNO	5
PROCNO	1
Date_	20120730
Time	9.04
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	287.4
DW	139.200 usec
DE	54.00 usec
TE	294.2 K
D1	5.00000000 sec
TD0	1

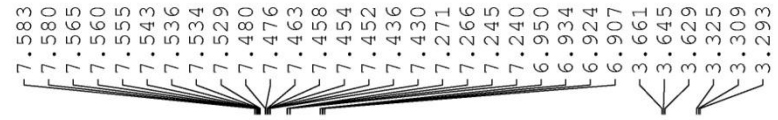
======== CHANNEL f1 ========

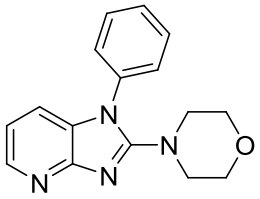
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300064 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00


159.930
154.287
143.453
128.056
118.132
116.680
77.571
77.148
76.724
66.508
54.788
51.013
35.381
28.776
N
N
N
N
O
200
180
160
140
120
100
80
60
40
20
ppm

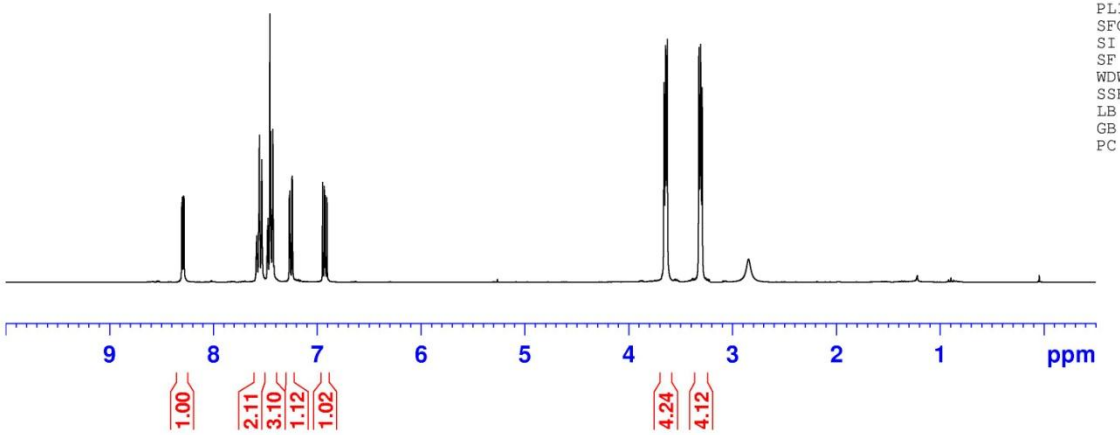
56

AJ-1-66
after column (final)



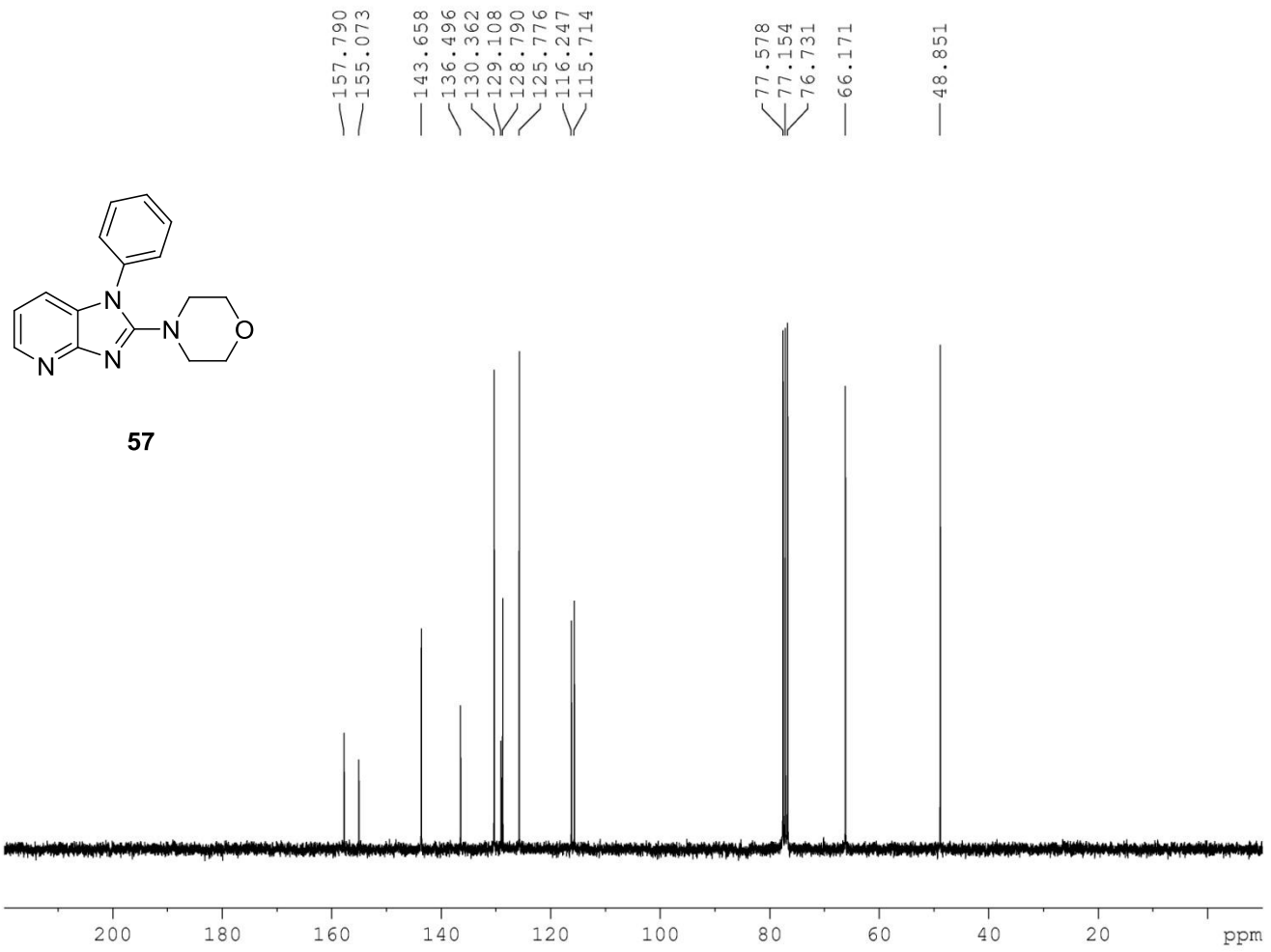


57



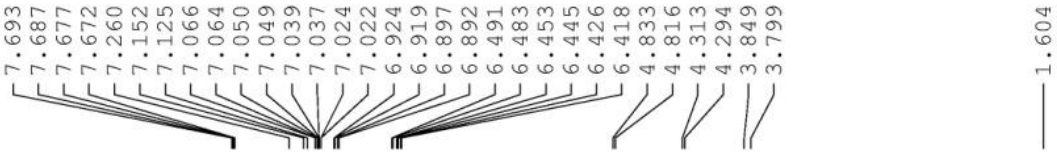
BRUKER

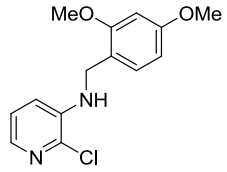
NAME	AJ-1-66	
EXPNO	4	
PROCNO	1	
Date_	20120731	
Time	8.06	
INSTRUM	spect	
PROBHD	5 mm QNP 1H/1	
PULPROG	zg	
TD	32768	
SOLVENT	CDCl3	
NS	12	
DS	0	
SWH	3591.954	Hz
FIDRES	0.109618	Hz
AQ	4.5613556	sec
RG	35.9	
DW	139.200	usec
DE	54.00	usec
TE	295.2	K
D1	5.00000000	sec
TD0	1	
======== CHANNEL f1 ========		
NUC1	1H	
P1	9.75	usec
PL1	0.00	dB
SFO1	300.1315007	MHz
SI	32768	
SF	300.1300061	MHz
WDW	EM	
SSB	0	
LB	0.20	Hz
GB	0	
PC	1.00	


157.790
155.073
143.658
136.496
130.362
129.108
128.790
125.776
116.247
115.714
77.578
77.154
76.731
66.171
48.851
N
N
N
N
O
200
180
160
140
120
100
80
60
40
20
ppm

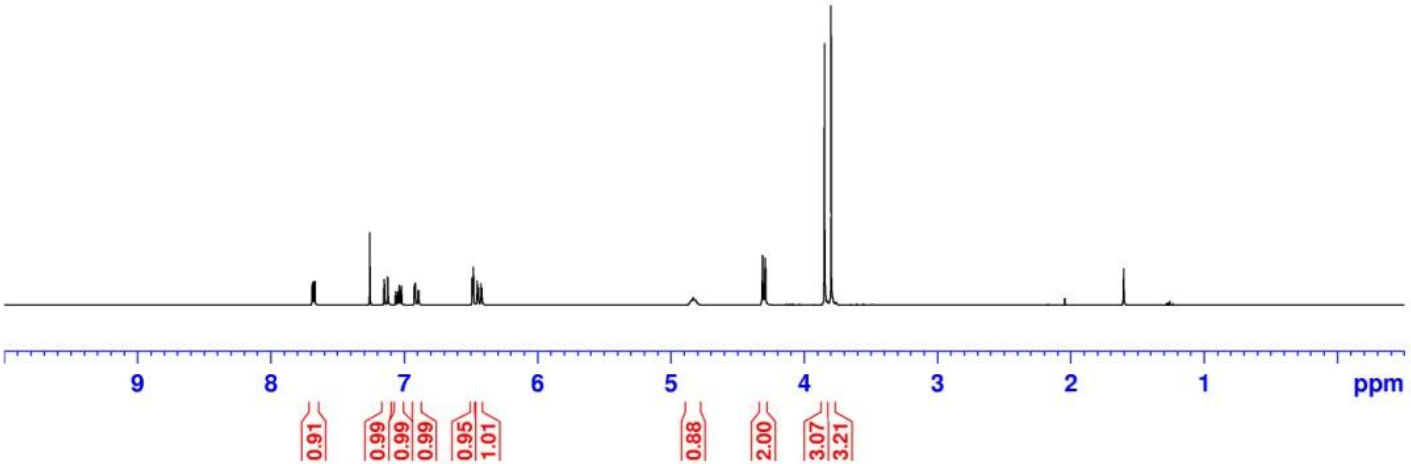
57

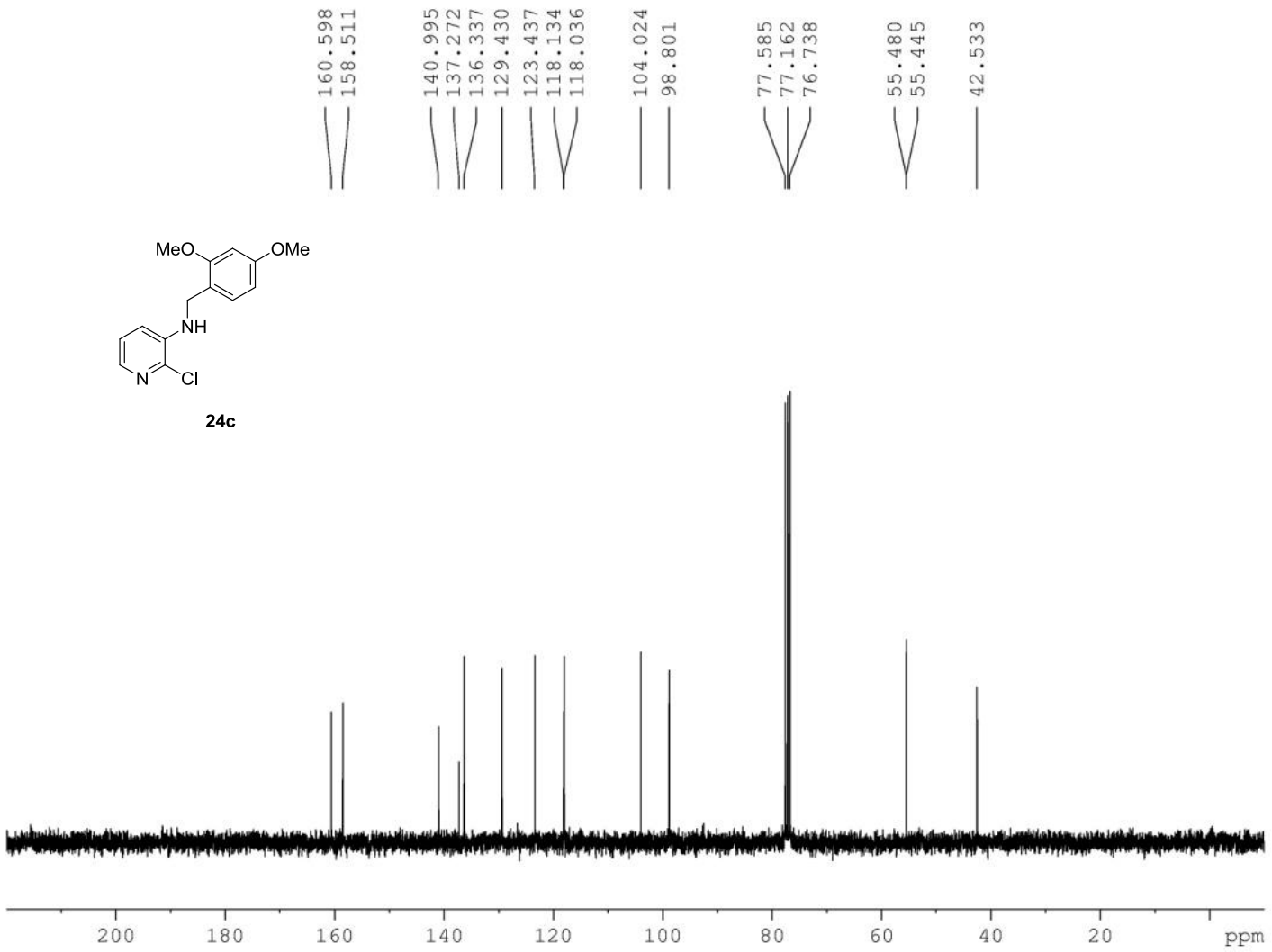
9.4 SYNTHESIS

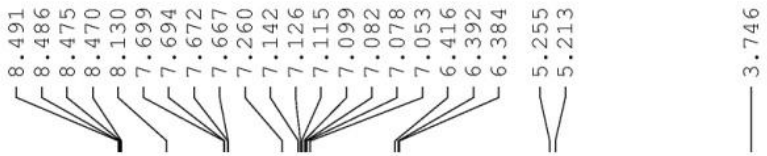

7.693
7.687
7.677
7.672
7.260
7.152
7.125
7.066
7.064
7.050
7.049
7.039
7.037
7.024
7.022
6.924
6.919
6.897
6.892
6.491
6.483
6.453
6.445
6.426
6.418
4.833
4.816
4.313
4.294
3.849
3.799
1.604

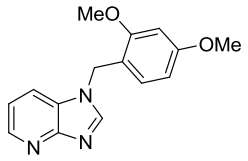

MeO
OMe
NH
N
Cl

24c

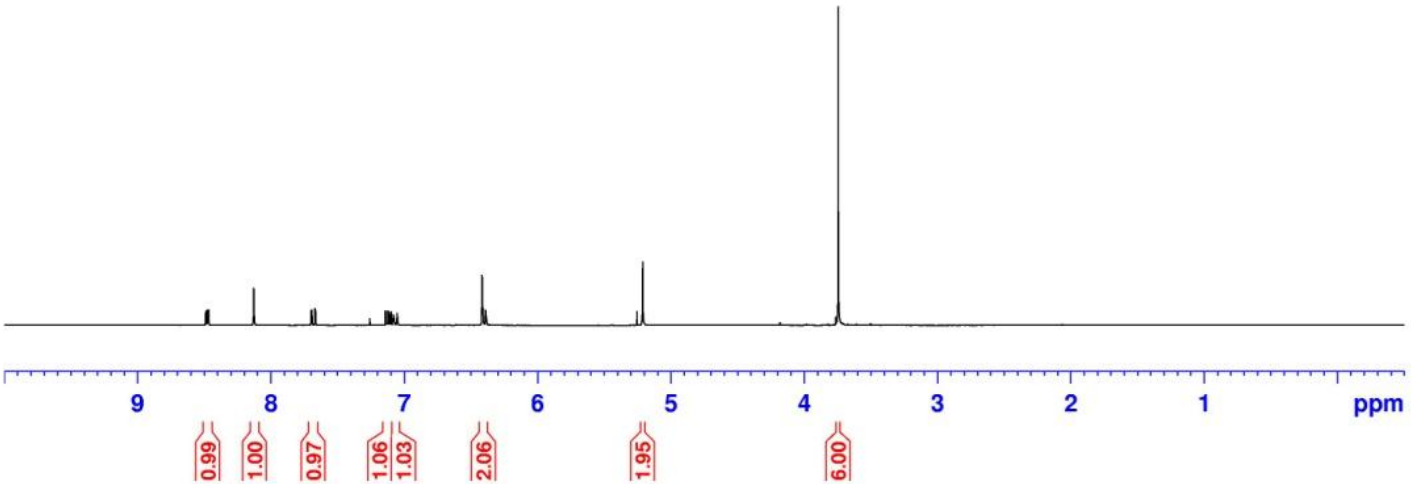

9
8
7
6
5
4
3
2
1
ppm
0.91
0.99
0.99
0.99
0.95
1.01
0.88
2.00
3.07
3.21

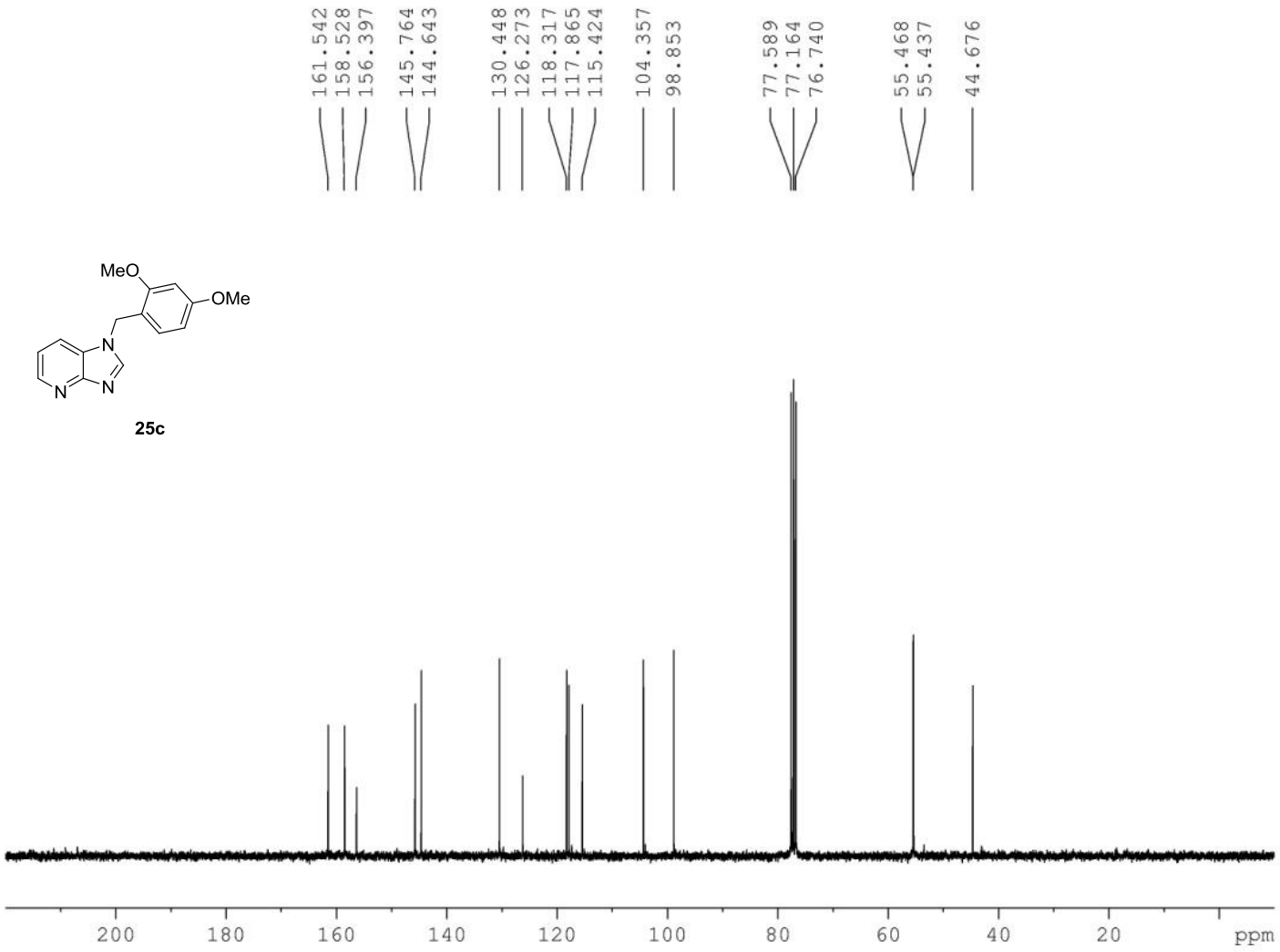

160.598
158.511
140.995
137.272
136.337
129.430
123.437
118.134
118.036
104.024
98.801
77.585
77.162
76.738
55.480
55.445
42.533
MeO
OMe
NH
N
Cl
24c
200
180
160
140
120
100
80
60
40
20
ppm


8.491
8.486
8.475
8.470
8.130
7.699
7.694
7.672
7.667
7.260
7.142
7.126
7.115
7.099
7.082
7.078
7.053
6.416
6.392
6.384
5.255
5.213
3.746

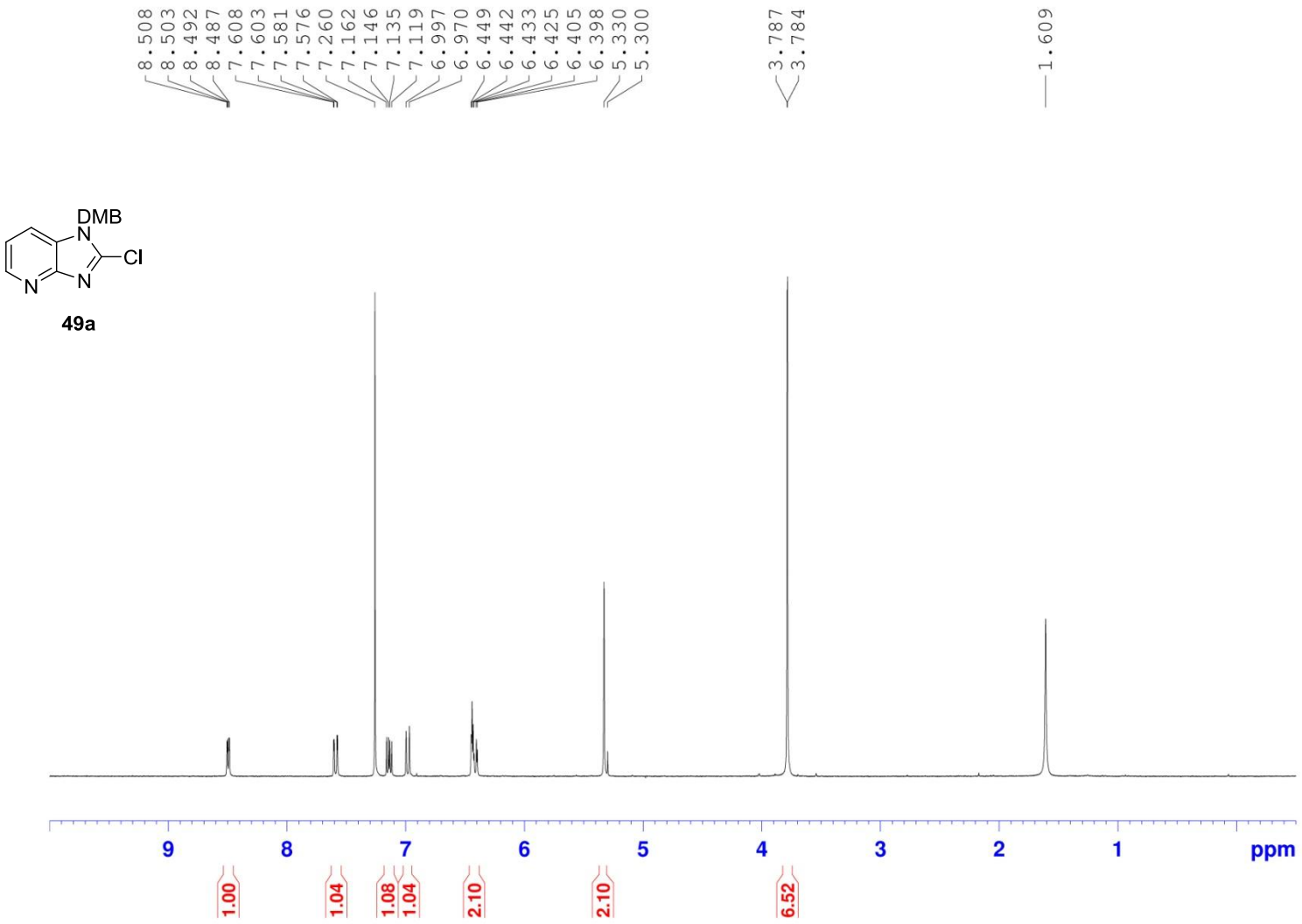

MeO
OMe
N
N
N

25c

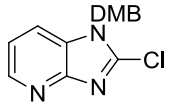

9
8
7
6
5
4
3
2
1
ppm
0.99
1.00
0.97
1.06
1.03
2.06
1.95
6.00


161.542
158.528
156.397
145.764
144.643
130.448
126.273
118.317
117.865
115.424
104.357
98.853
77.589
77.164
76.740
55.468
55.437
44.676
MeO
OMe
N
N
N
200
180
160
140
120
100
80
60
40
20
ppm

25c

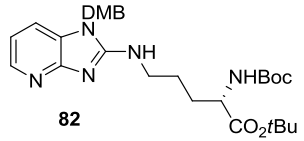

8.508
8.503
8.492
8.487
7.608
7.603
7.581
7.576
7.260
7.162
7.146
7.135
7.119
6.997
6.970
6.449
6.442
6.433
6.425
6.405
6.398
5.330
5.300
3.787
3.784
1.609
DMB
N
Cl
N
N
9
8
7
6
5
4
3
2
1
ppm
1.00
1.04
1.08
1.04
2.10
2.10
6.52

49a


DMB
N
Cl
N
N

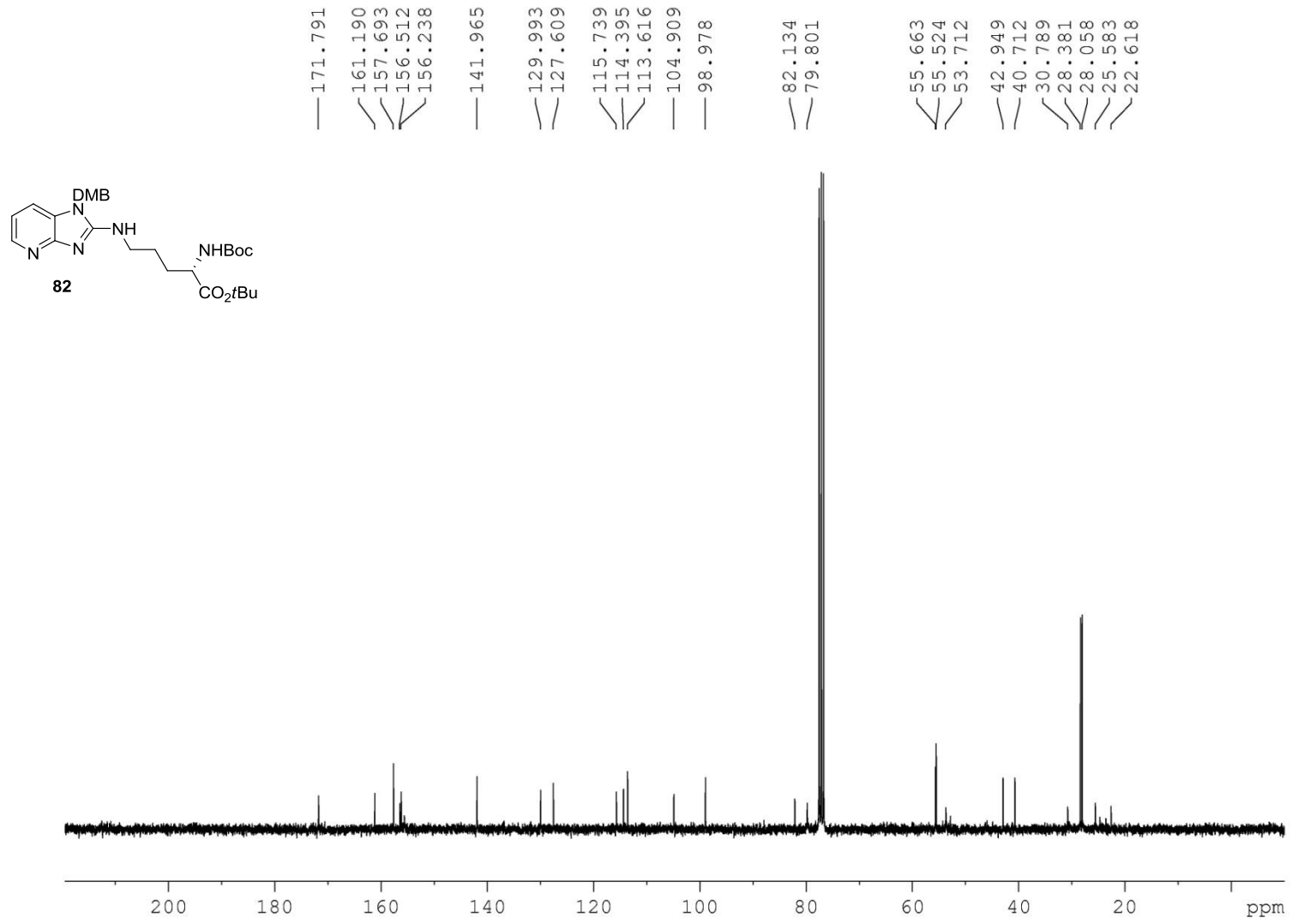
49a

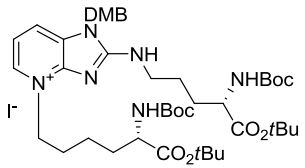
161.244
158.143
153.900
144.847
144.283
129.848
128.006
118.476
118.206
114.746
104.228
98.541
77.585
77.161
76.737
55.367
55.256
43.825
200
180
160
140
120
100
80
60
40
20
ppm


DMB
N
NH
N
NHBoc
CO2tBu

82

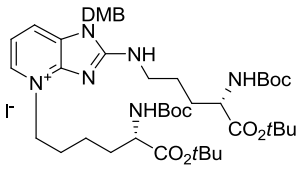
8.191
8.186
8.174
8.169
7.327
7.303
7.260
7.020
6.992
6.896
6.879
6.870
6.853
6.486
6.478
6.440
6.432
6.412
6.404
5.340
5.151
5.124
4.961
4.210
4.185
4.167
3.859
3.780
3.615
3.596
1.849
1.831
1.814
1.782
1.759
1.736
1.713
1.695
1.683
1.670
1.645
1.621
1.432
1.412
9
8
7
6
5
4
3
2
1
ppm
1.00
1.01
1.01
1.03
0.98
1.05
0.87
1.00
2.03
1.02
3.05
3.11
2.02
4.77
9.33
9.03


171.791
161.190
157.693
156.512
156.238
141.965
129.993
127.609
115.739
114.395
113.616
104.909
98.978
82.134
79.801
55.663
55.524
53.712
42.949
40.712
30.789
28.381
28.058
25.583
22.618
DMB
N
NH
N
N
NHBoc
CO2tBu
82
200
180
160
140
120
100
80
60
40
20
ppm


DMB
N
NH
N
N+
I-
NHBoc
NHBoc
CO2tBu
CO2tBu

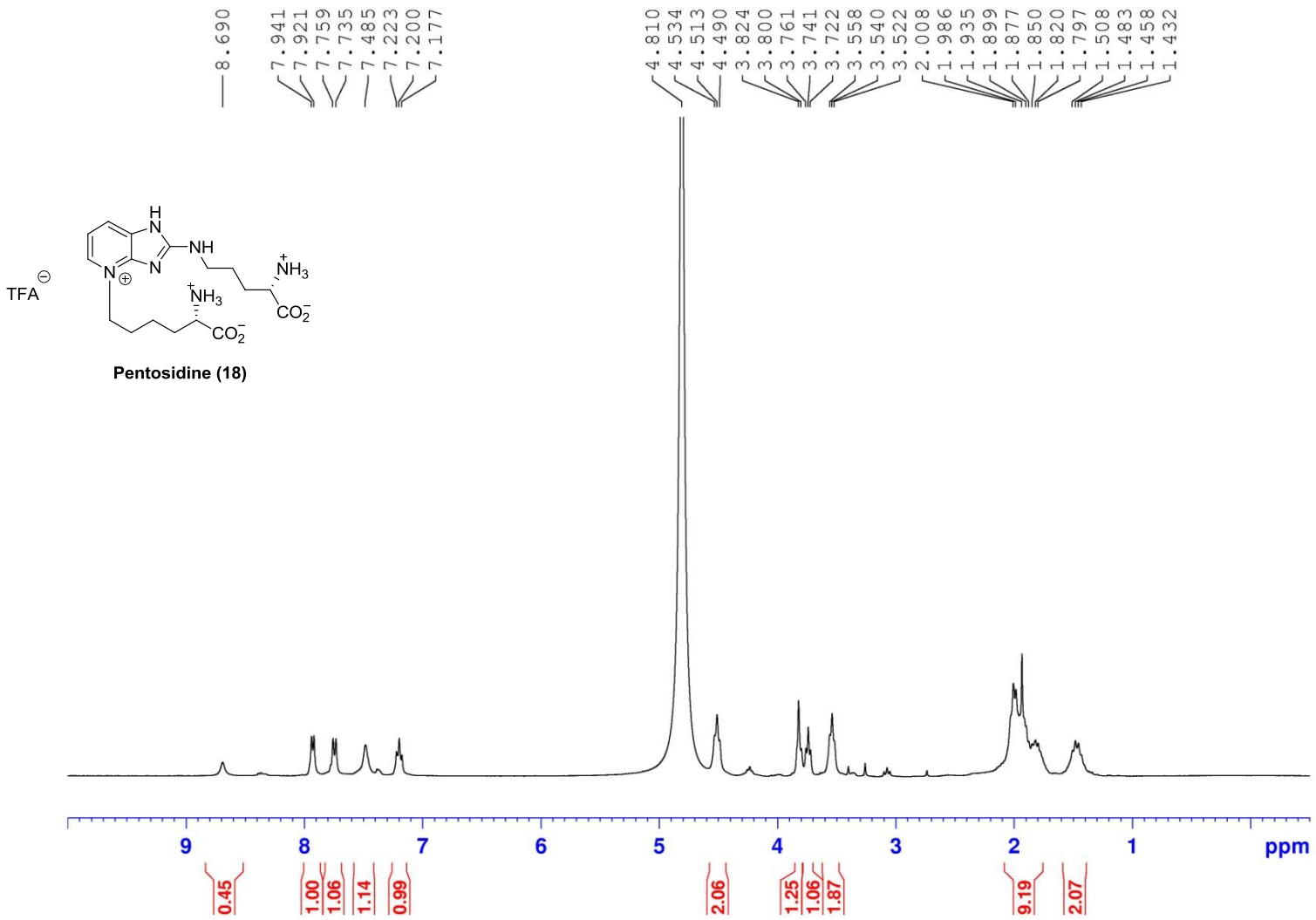
89

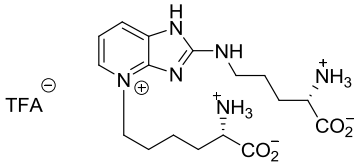
7.953
7.628
7.603
7.473
7.446
7.260
7.077
7.053
7.029
6.316
6.288
6.254
5.311
5.167
5.142
5.098
5.075
4.435
4.046
3.976
3.961
3.650
3.617
1.866
1.732
1.615
1.586
1.562
1.537
1.514
1.488
1.482
1.270
9
8
7
6
5
4
3
2
1
ppm
1.97
1.06
0.97
0.93
1.01
1.00
2.04
0.94
0.73
1.76
2.09
2.99
3.18
10.45
37.89


DMB
N
NH
N
N+
I-
NHBoc
NHBoc
CO2tBu
CO2tBu

89

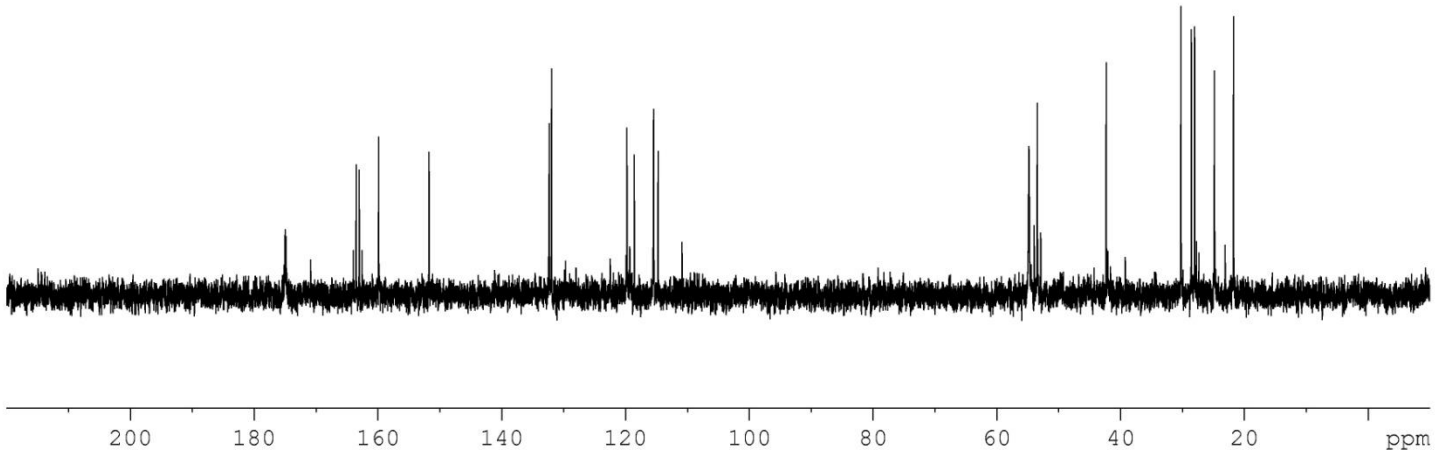
171.415
171.332
161.195
158.849
157.930
155.280
155.213
150.946
132.608
131.647
131.212
118.451
114.380
113.842
104.575
98.391
81.549
79.279
55.524
55.210
53.403
52.609
42.657
42.449
41.514
31.887
29.669
28.645
28.037
27.674
25.236
22.030
200
180
160
140
120
100
80
60
40
20
ppm


8.690
7.941
7.921
7.759
7.735
7.485
7.223
7.200
7.177
4.810
4.534
4.513
4.490
3.824
3.800
3.761
3.741
3.722
3.558
3.540
3.522
2.008
1.986
1.935
1.899
1.877
1.850
1.820
1.797
1.508
1.483
1.458
1.432
TFA
Pentosidine (18)
9
8
7
6
5
4
3
2
1
ppm
0.45
1.00
1.06
1.14
0.99
2.06
1.25
1.06
1.87
9.19
2.07



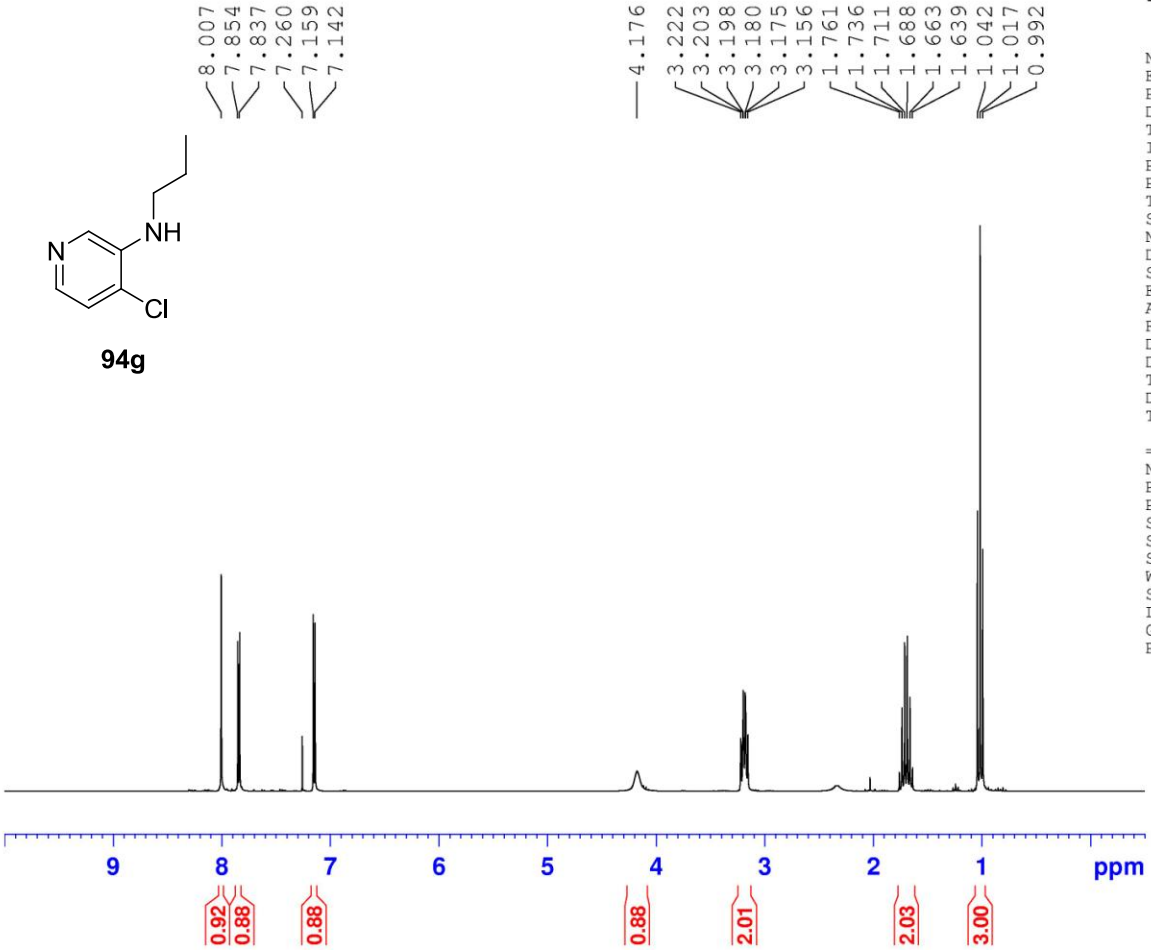
Pentosidine (18)

174.952
174.848
163.962
163.492
163.022
162.529
159.863
151.699
132.358
131.970
122.486
119.799
118.619
115.514
114.783
110.886
54.895
54.773
53.472
42.345
30.308
28.630
28.081
24.842
21.776



9.5 IMIDAZO[4,5-C]PYRIDINES

AJR-5-062
Post Pump

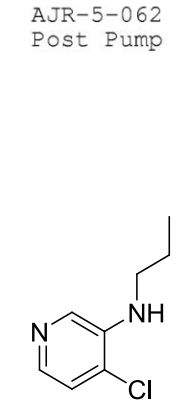


94g

BRUKER

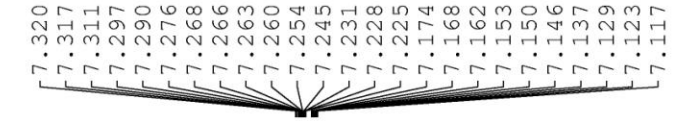
NAME	AJR-5-062
EXPNO	5
PROCNO	1
Date_	20120717
Time	10.06
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	161.3
DW	139.200 usec
DE	54.00 usec
TE	294.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300062 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

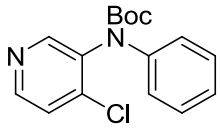
AJR-5-062
Post Pump



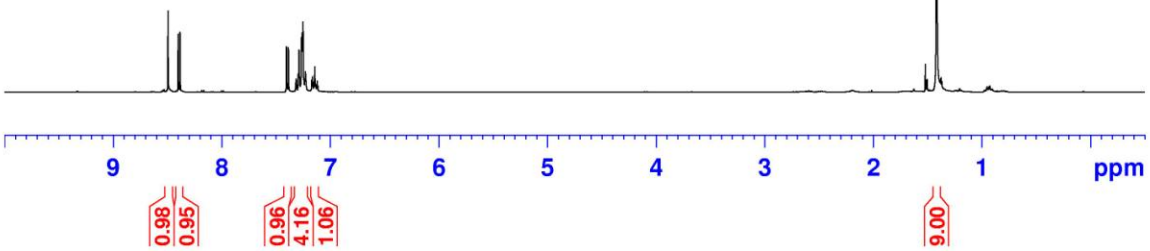
94g

AJR-6-149
Post Column



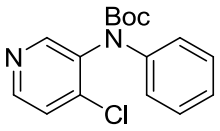


95h



NAME	AJR-6-149
EXPNO	2
PROCNO	1
Date_	20130620
Time	16.45
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	50.8
DW	139.200 usec
DE	54.00 usec
TE	298.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300061 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

AJR-6-149
Post Column

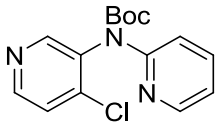


95h

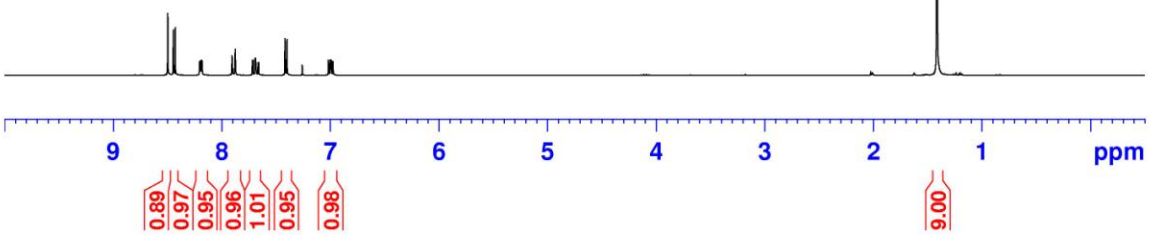
AJR-6-175
Post Column

8.182 7.906 7.881 7.878 7.875 7.720 7.713 7.696 7.692 7.689 7.686 7.668 7.661 7.420 7.419 7.402 7.401 7.260 7.020 7.017 7.004 7.000 6.995 6.992 6.979 6.976

1.414



SI5

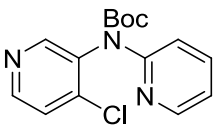


BRUKER

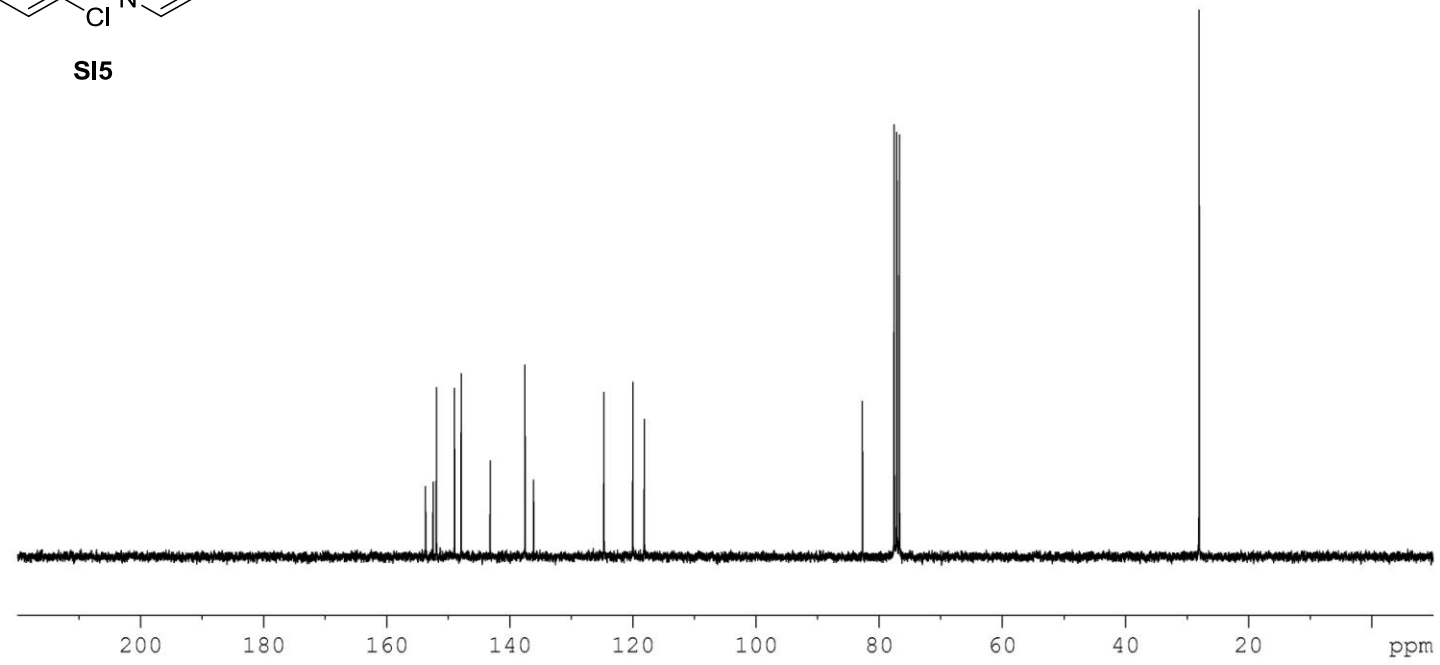
NAME	AJR-6-175
EXPNO	2
PROCNO	1
Date_	20130709
Time	17.14
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	64
DW	139.200 usec
DE	54.00 usec
TE	295.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300061 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

AJR-6-175
Post Column

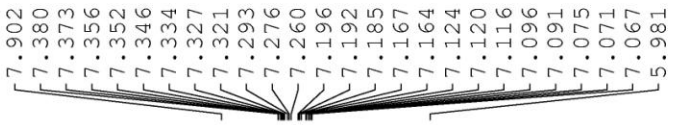
153.735
152.512
151.964
149.040
147.948
143.219
137.585
136.176
124.744
120.040
118.192
82.734
77.591
77.167
76.743
28.043

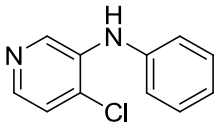


SI5

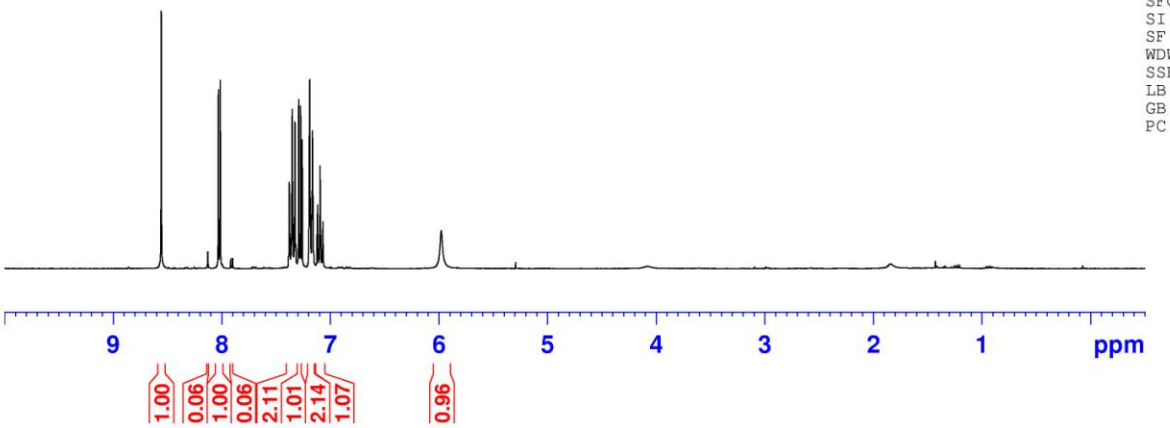


AJR-6-177
Crude





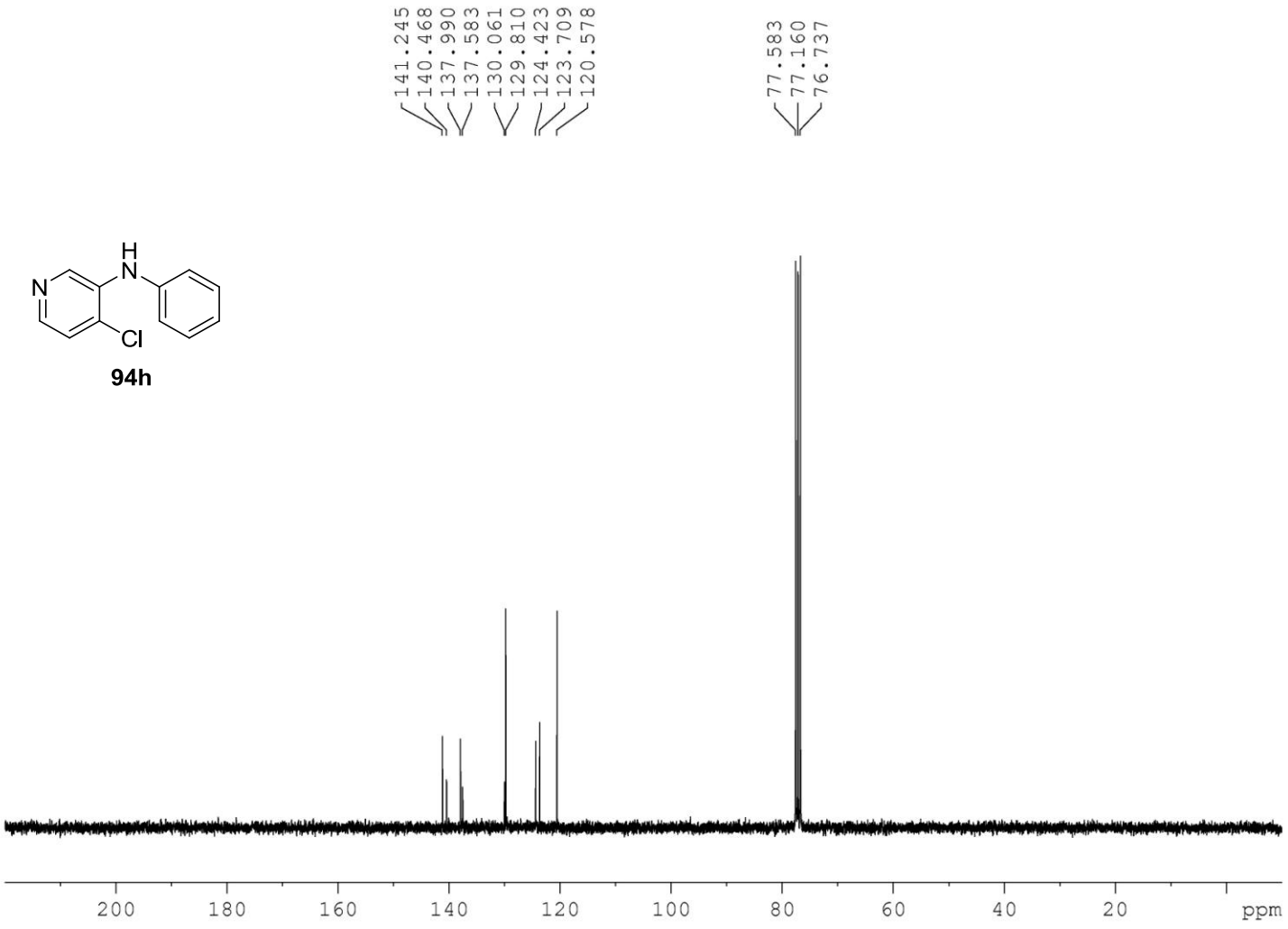
94h



BRUKER

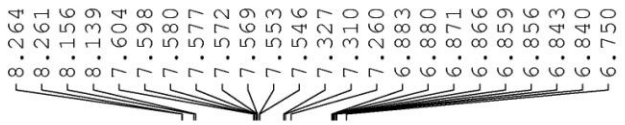
NAME	AJR-6-177
EXPNO	1
PROCNO	1
Date_	20130709
Time	18.02
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	322.5
DW	139.200 usec
DE	54.00 usec
TE	295.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300061 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

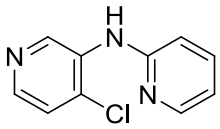
AJR-6-177


141.245
140.468
137.990
137.583
130.061
129.810
124.423
123.709
120.578
77.583
77.160
76.737
H
N
N
Cl
200
180
160
140
120
100
80
60
40
20
ppm

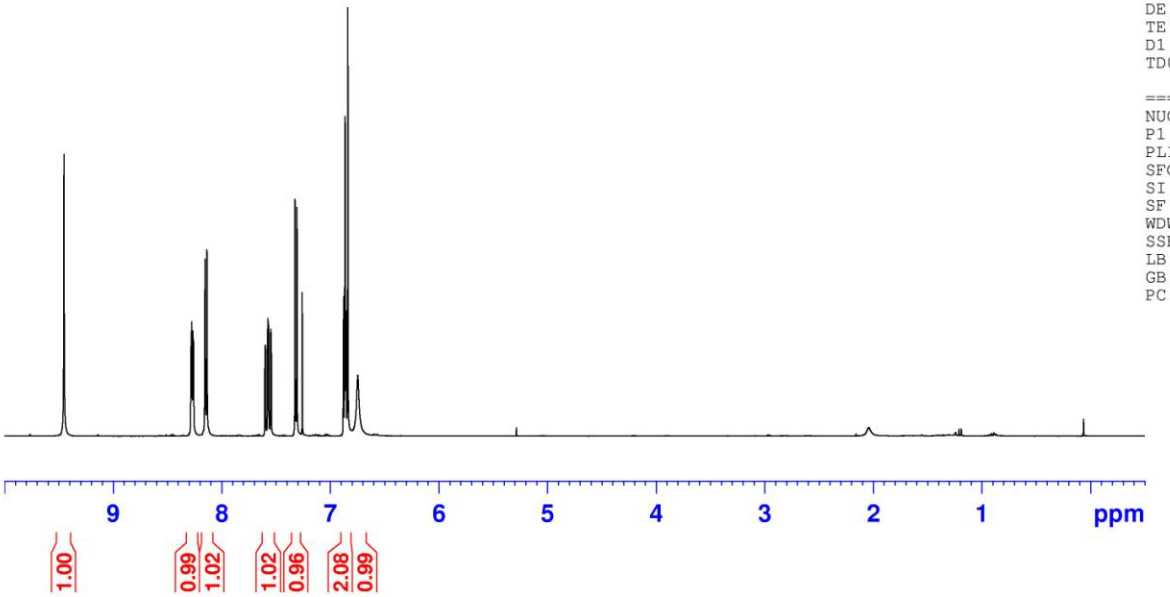
94h

AJR-6-178





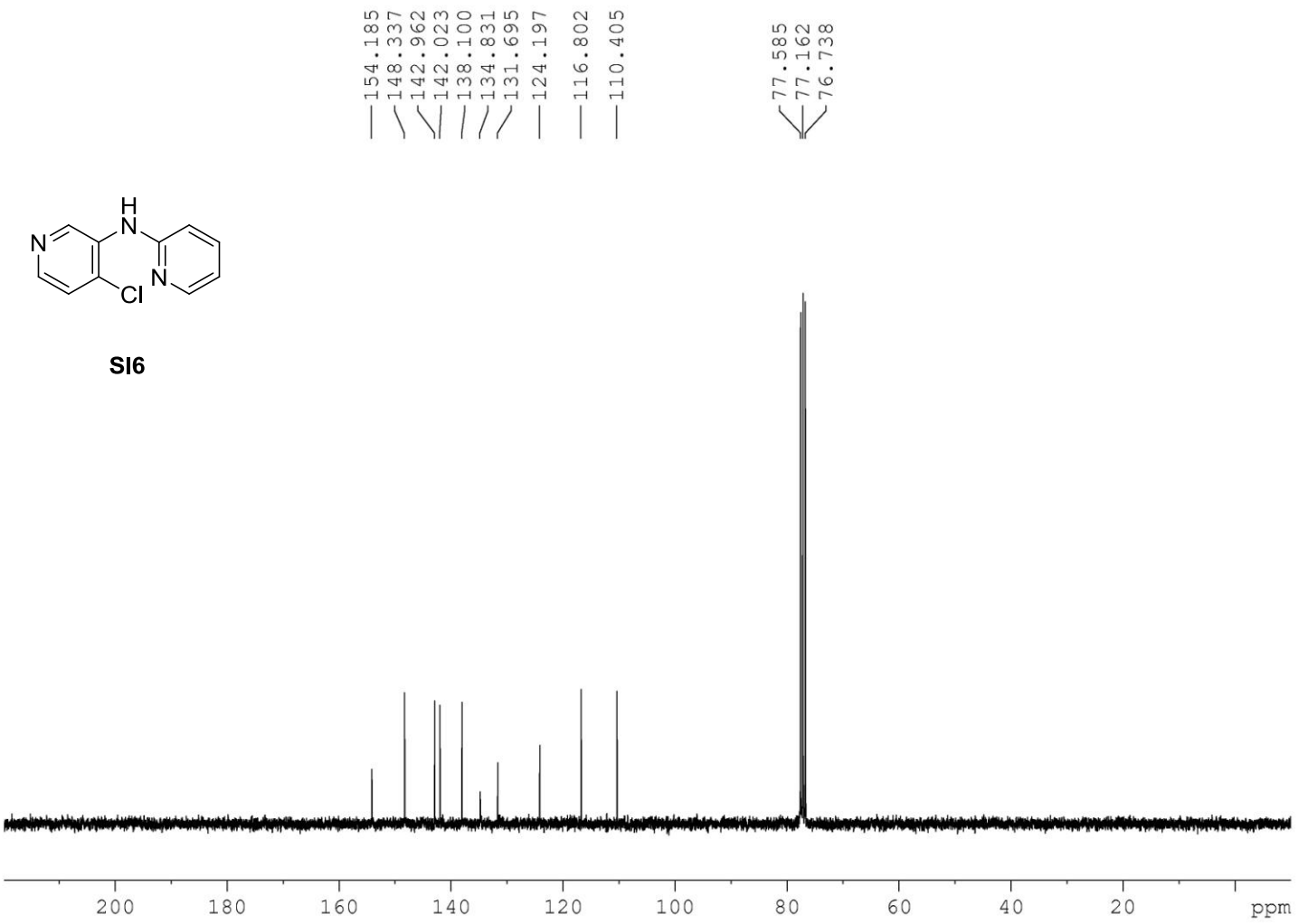
SI6



BRUKER

NAME	AJR-6-178
EXPNO	1
PROCNO	1
Date_	20130711
Time	10.03
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	287.4
DW	139.200 usec
DE	54.00 usec
TE	295.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300062 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

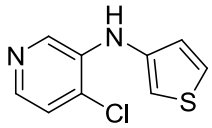
AJR-6-178


154.185
148.337
142.962
142.023
138.100
134.831
131.695
124.197
116.802
110.405
77.585
77.162
76.738
H
N
N
N
Cl
200
180
160
140
120
100
80
60
40
20
ppm

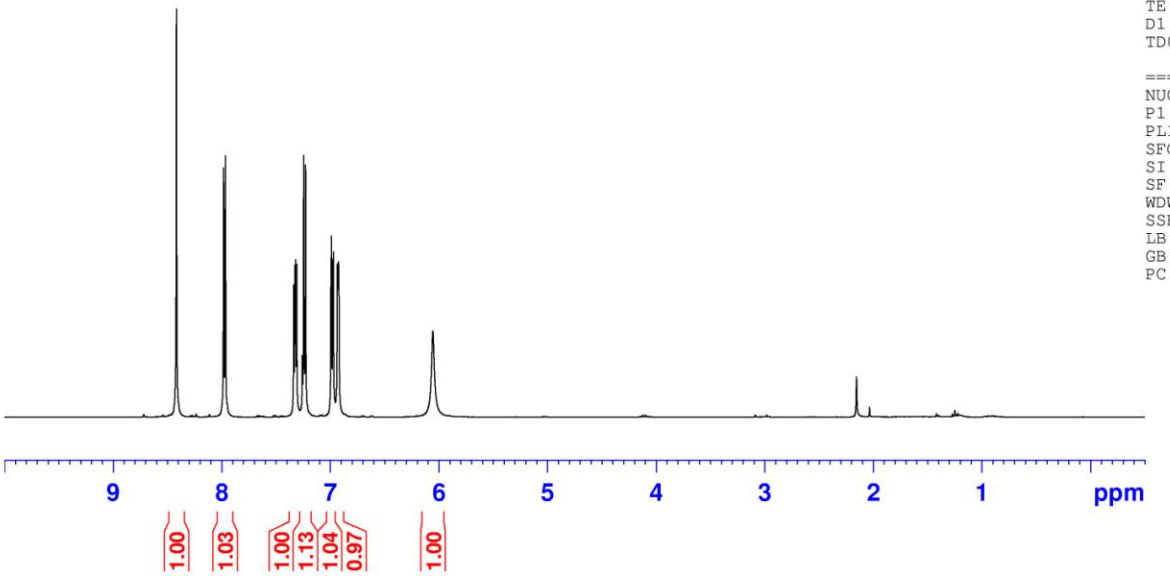
SI6

AJR-6-180
Post Column

8.419
7.985
7.968
7.339
7.329
7.322
7.312
7.260
7.247
7.230
6.996
6.991
6.979
6.974
6.937
6.934
6.932
6.927
6.924
6.058



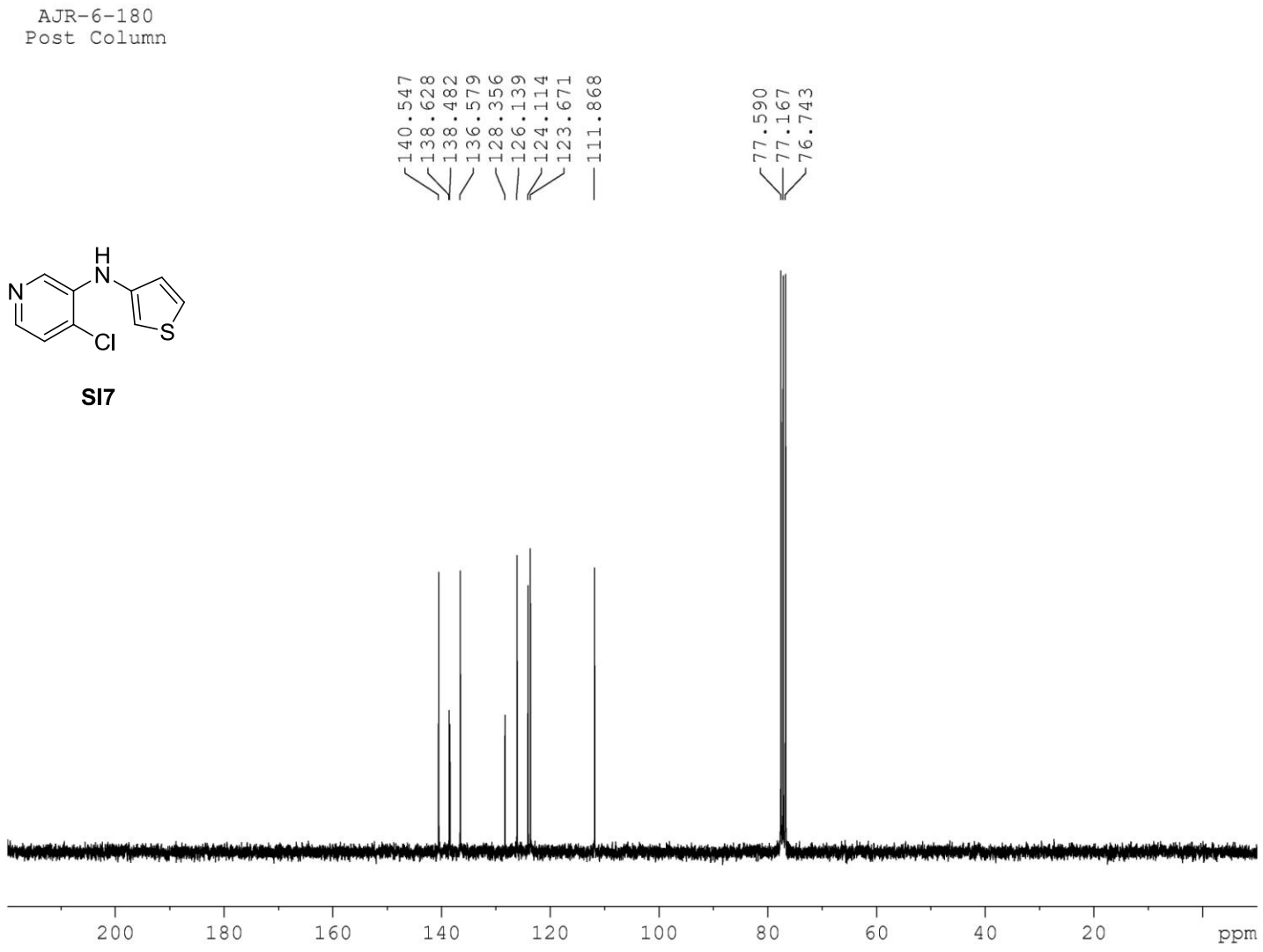
SI7



BRUKER

NAME	AJR-6-180
EXPNO	2
PROCNO	1
Date_	20130711
Time	16.46
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	181
DW	139.200 usec
DE	54.00 usec
TE	295.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300061 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

AJR-6-180
Post Column

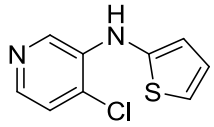


SI7

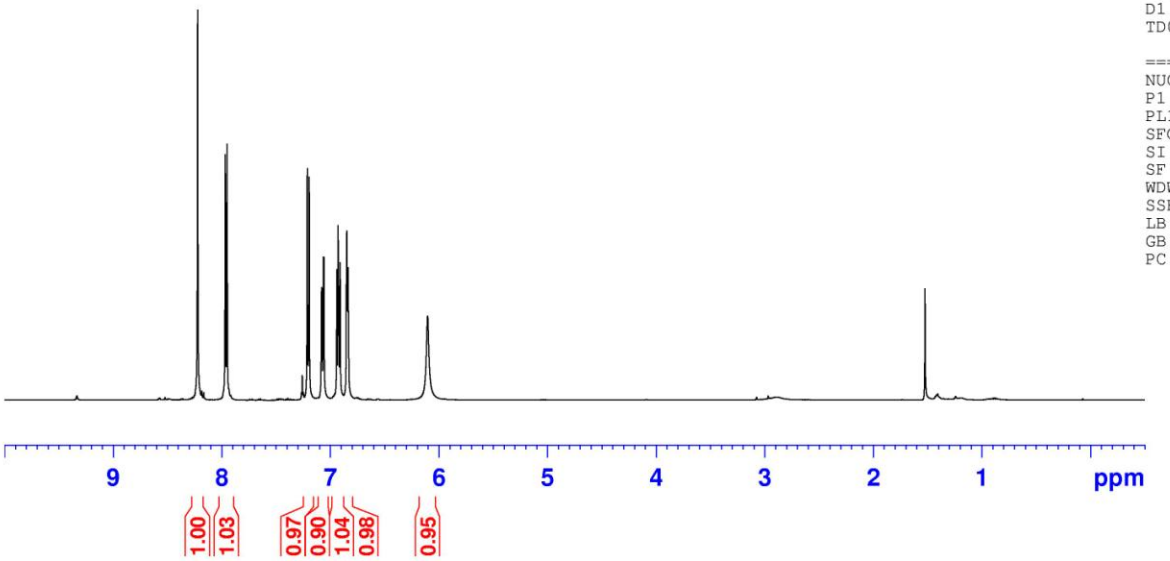
AJR-6-190

8.224 7.970 7.953 7.260 7.214 7.197 7.084 7.080 7.065 7.061 6.943 6.930 6.924 6.912 6.854 6.850 6.847 6.842 6.838 6.835 6.106

1.525



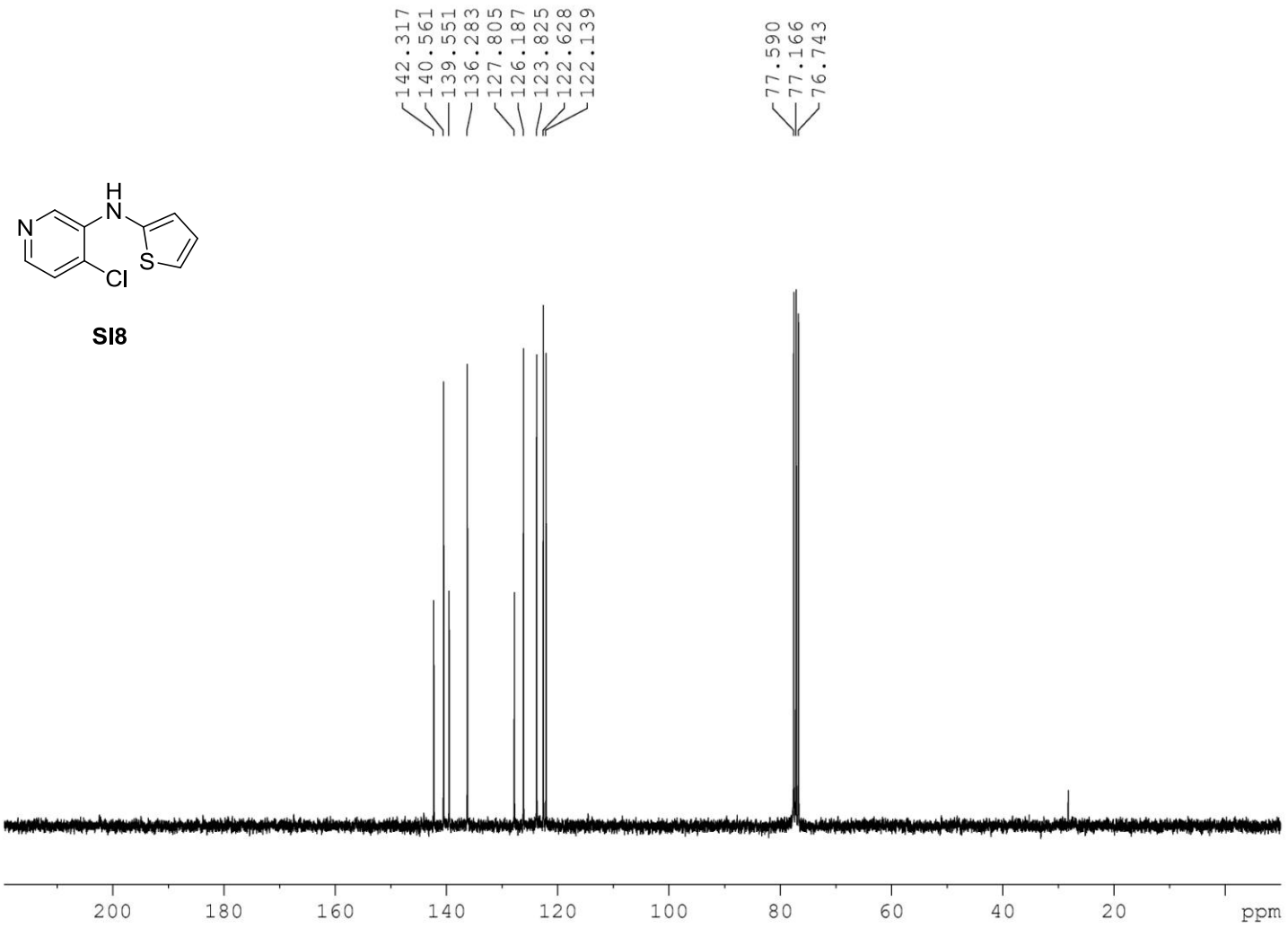
SI8



BRUKER

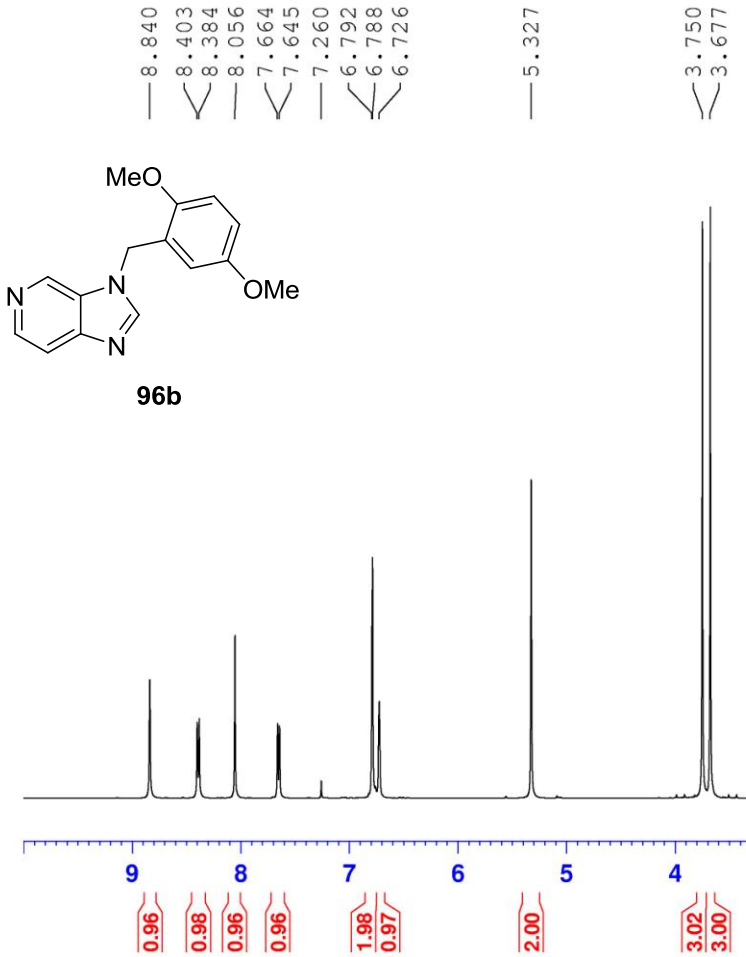
NAME	AJR-6-190
EXPNO	2
PROCNO	1
Date_	20130724
Time	18.14
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	101.6
DW	139.200 usec
DE	54.00 usec
TE	683.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300061 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

AJR-6-190


142.317
140.561
139.551
136.283
127.805
126.187
123.825
122.628
122.139
77.590
77.166
76.743
H
N
N
S
Cl
200
180
160
140
120
100
80
60
40
20
ppm

SI8

AJR-6-013
Post Column



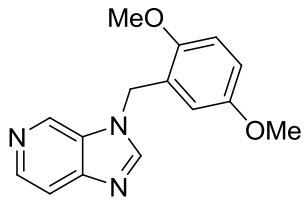
96b

BRUKER

NAME	AJR-6-013
EXPNO	3
PROCNO	1
Date_	20130308
Time	18.13
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	90.5
DW	139.200 usec
DE	54.00 usec
TE	298.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300060 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

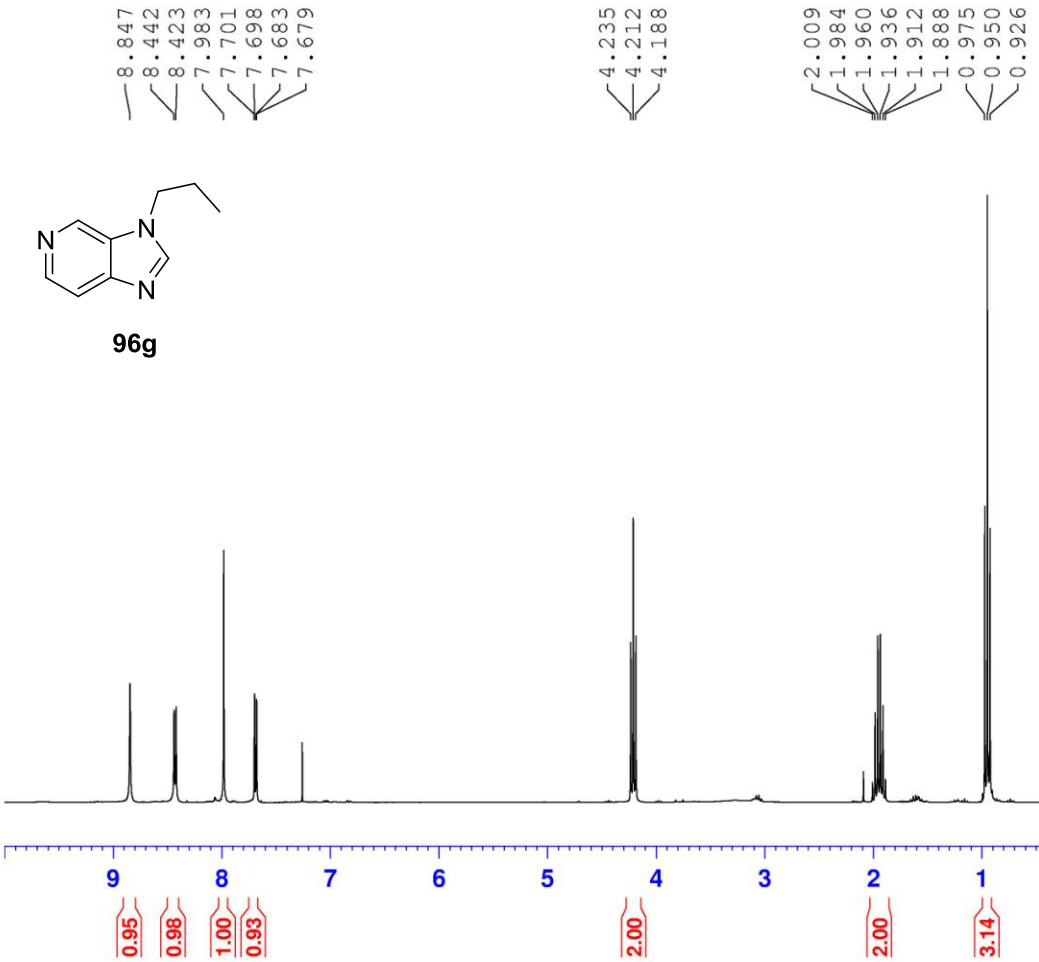
AJR-6-013
Post Column

153.643
151.462
148.826
146.338
141.797
133.875
131.757
123.749
116.192
114.992
114.146
111.716
77.589
77.165
76.741
55.802
55.773
44.958



96b

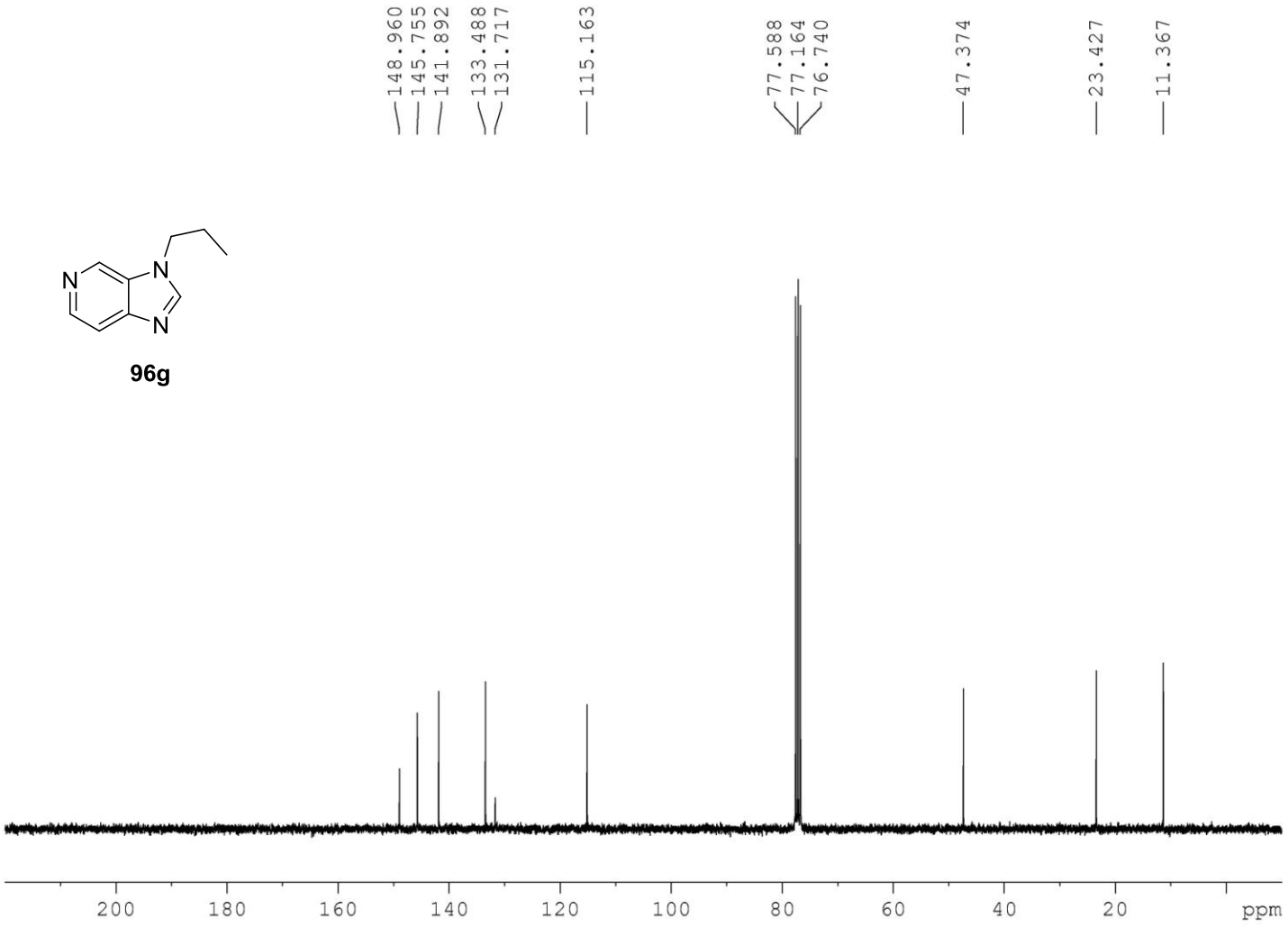
AJR-5-069
Post Column



96g

NAME	AJR-5-069
EXPNO	3
PROCNO	1
Date_	20120726
Time	12.55
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	143.7
DW	139.200 usec
DE	54.00 usec
TE	295.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300062 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

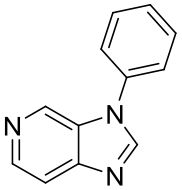
AJR-5-069


148.960
145.755
141.892
133.488
131.717
115.163
77.588
77.164
76.740
47.374
23.427
11.367
200
180
160
140
120
100
80
60
40
20
ppm

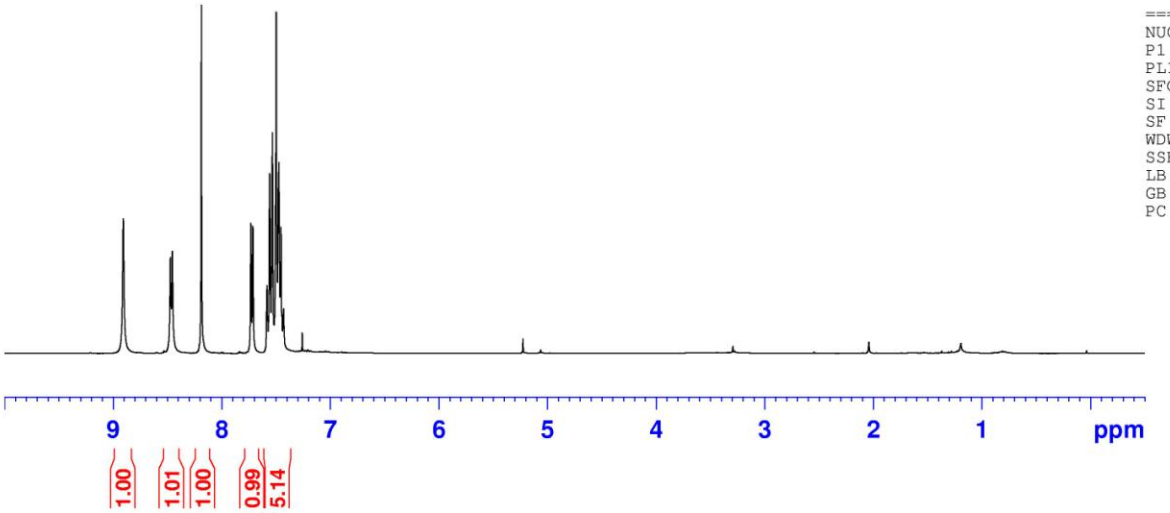
96g

AJR-6-179
Post Column

8.190
7.734
7.732
7.716
7.714
7.586
7.580
7.564
7.560
7.557
7.543
7.536
7.505
7.500
7.492
7.481
7.476
7.464
7.456
7.448
7.432
7.260



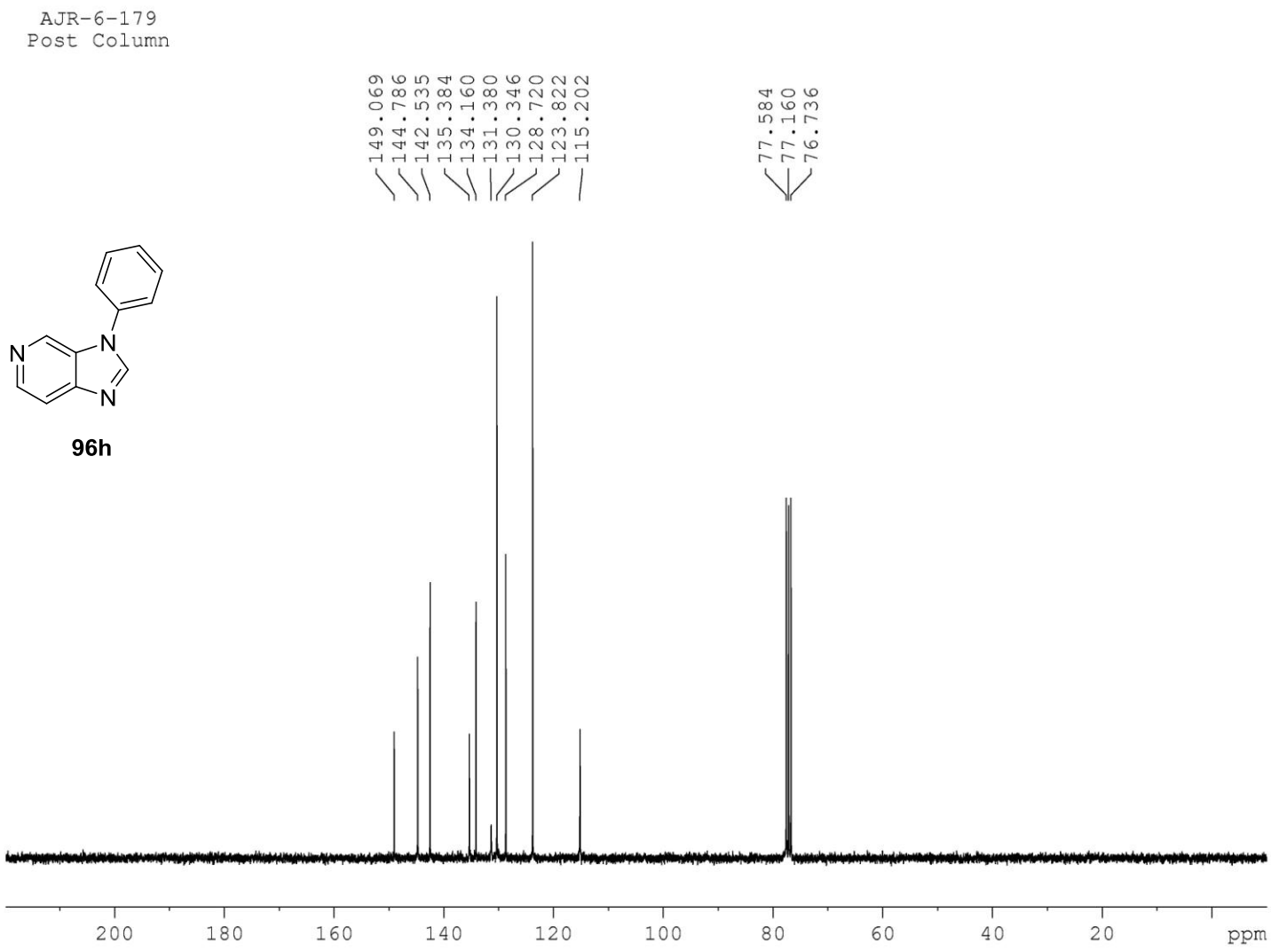
96h



BRUKER

NAME	AJR-6-179
EXPNO	1
PROCNO	1
Date_	20130710
Time	16.55
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	57
DW	139.200 usec
DE	54.00 usec
TE	295.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300060 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

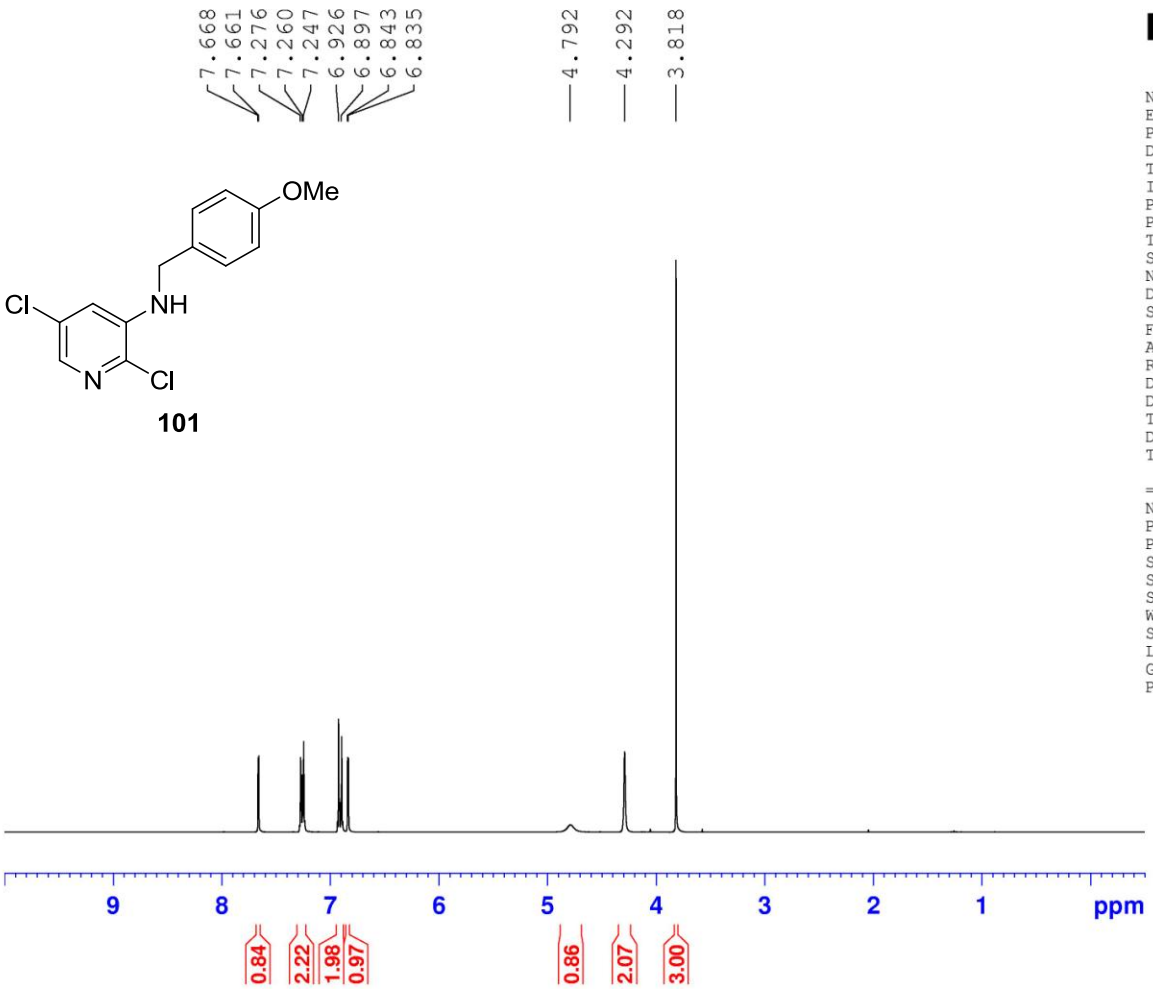
AJR-6-179
Post Column



96h

9.6 REGIOSELECTIVE AMIDATION OF POLYCHLORINATED AMINOPYRIDINES

AJR-5-217

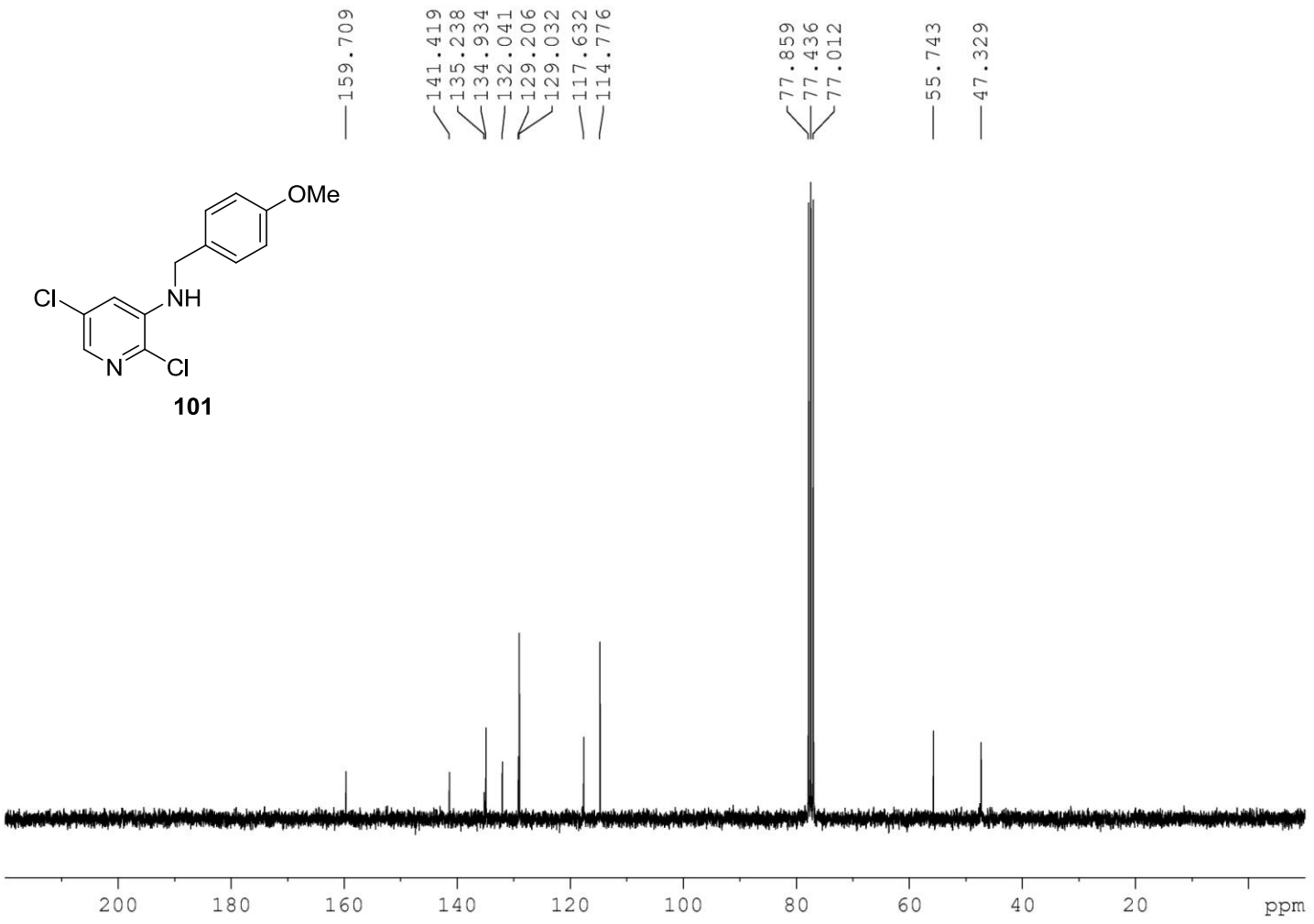


101

BRUKER

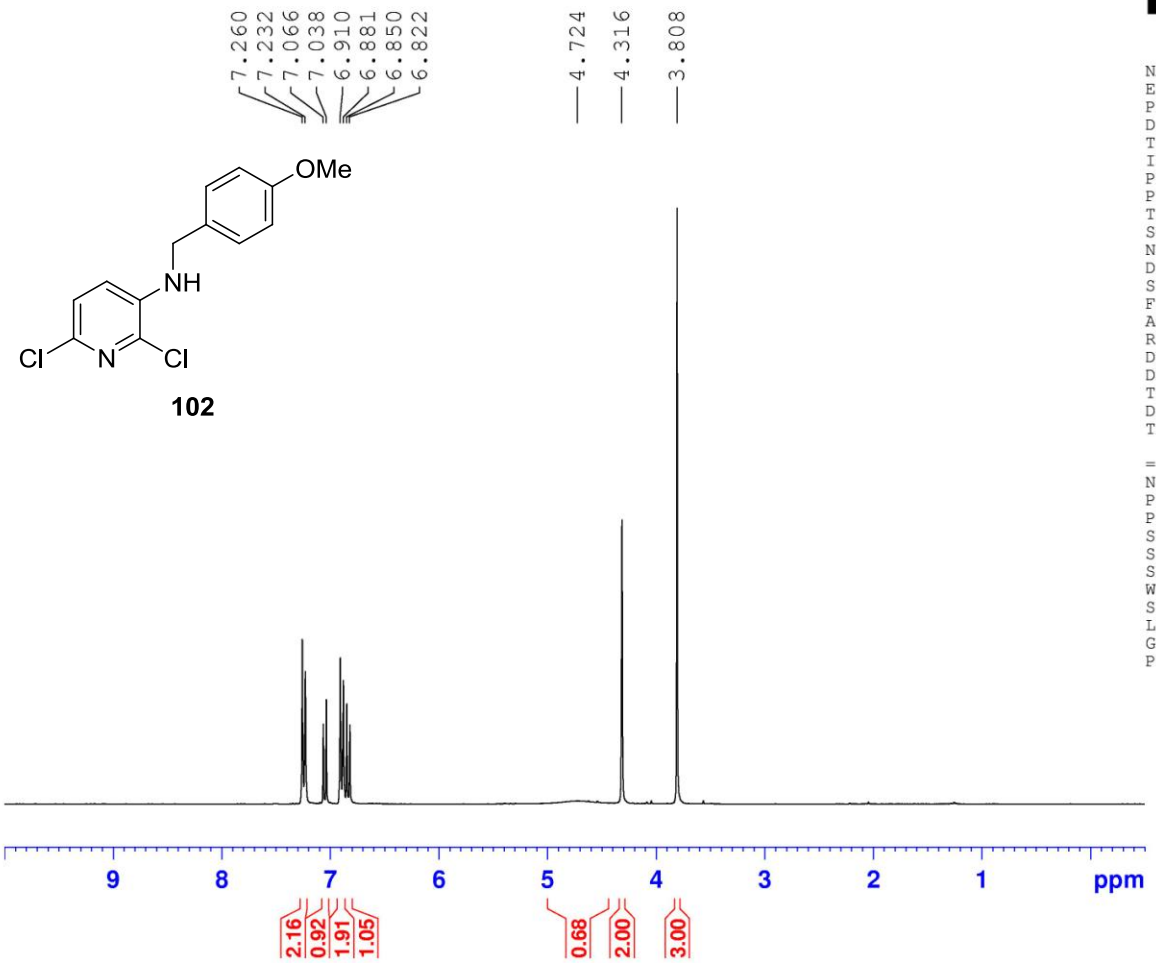
NAME	AJR-5-217
EXPNO	1
PROCNO	1
Date_	20121130
Time	9.27
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	256
DW	139.200 usec
DE	54.00 usec
TE	295.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300061 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

AJR-2-264
Post Recrystalization



101

TW-2-24
after recrystalization

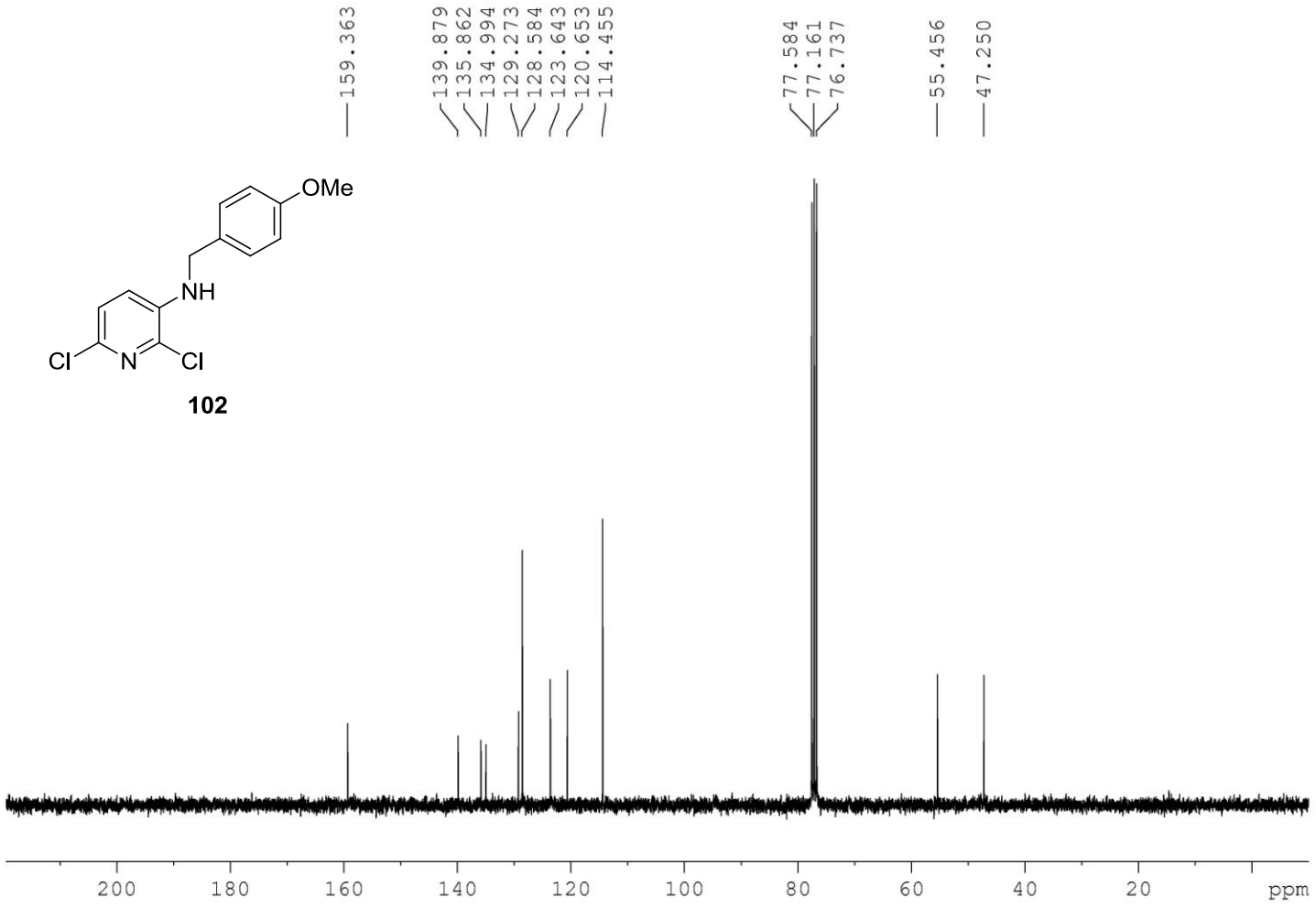


102

BRUKER

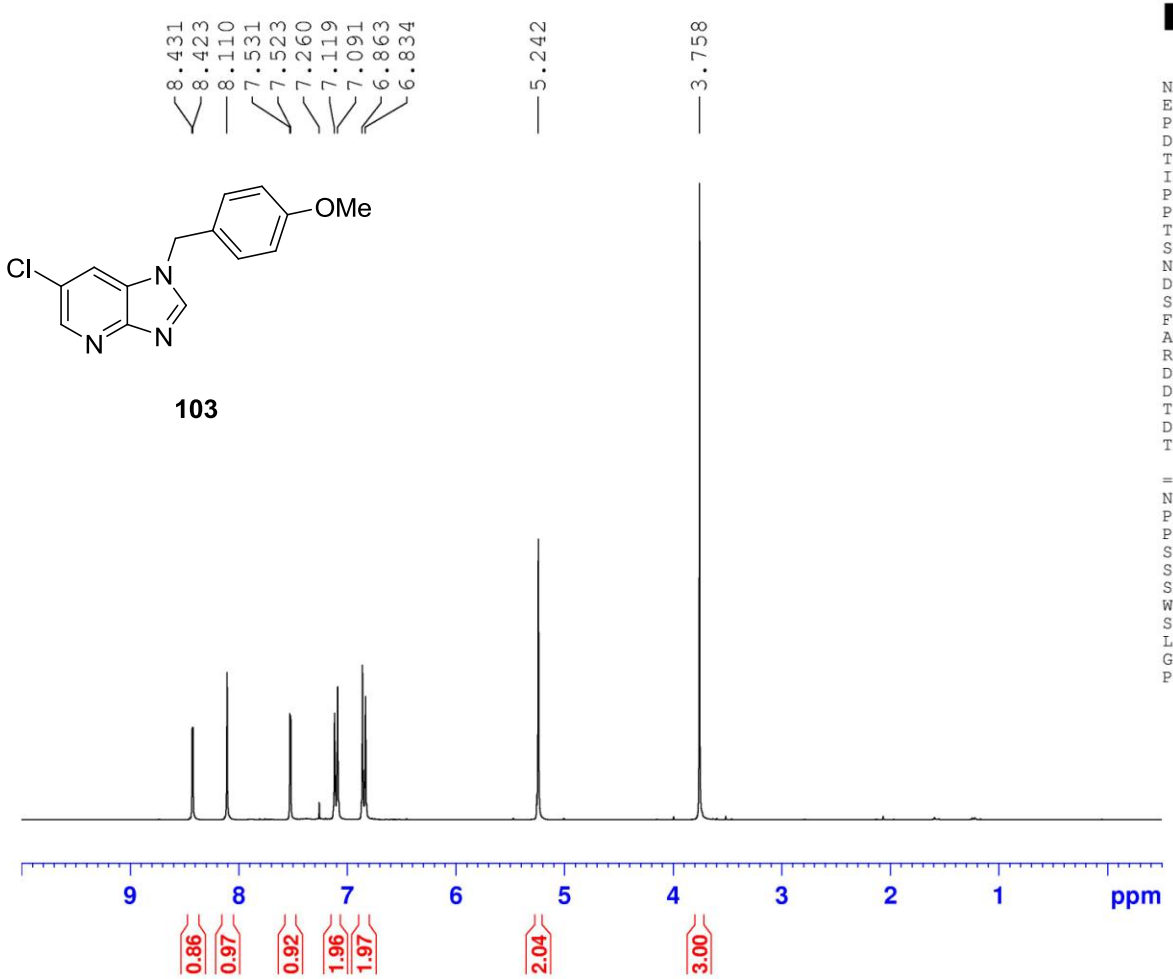
NAME	TW-2-24
EXPNO	1
PROCNO	1
Date_	20130220
Time	11.34
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	256
DW	139.200 usec
DE	54.00 usec
TE	297.2 K
D1	3.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300061 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

TW-2-24
carbon



102

AJR-5-240
Post Column



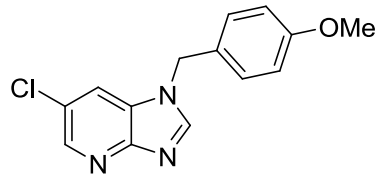
103

BRUKER

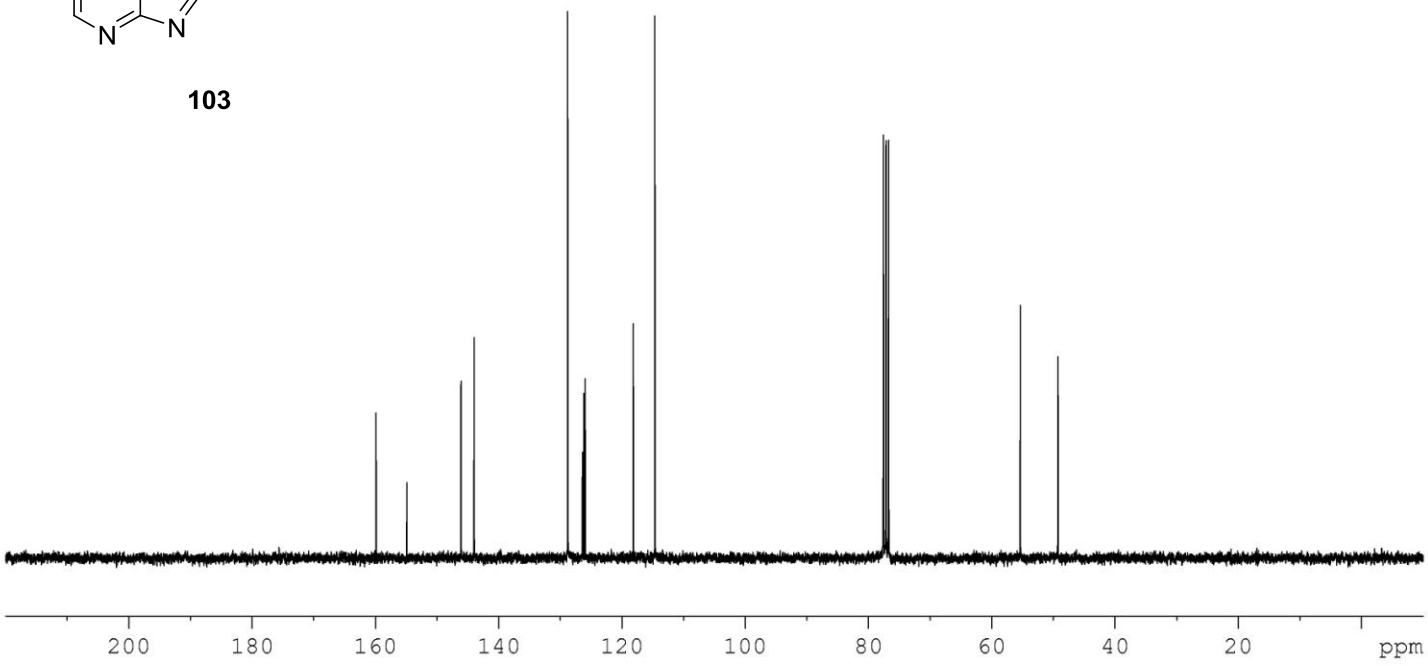
NAME	AJR-5-240
EXPNO	2
PROCNO	1
Date_	20121212
Time	18.10
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	71.8
DW	139.200 usec
DE	54.00 usec
TE	298.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300059 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

AJR-5-240
Post Column

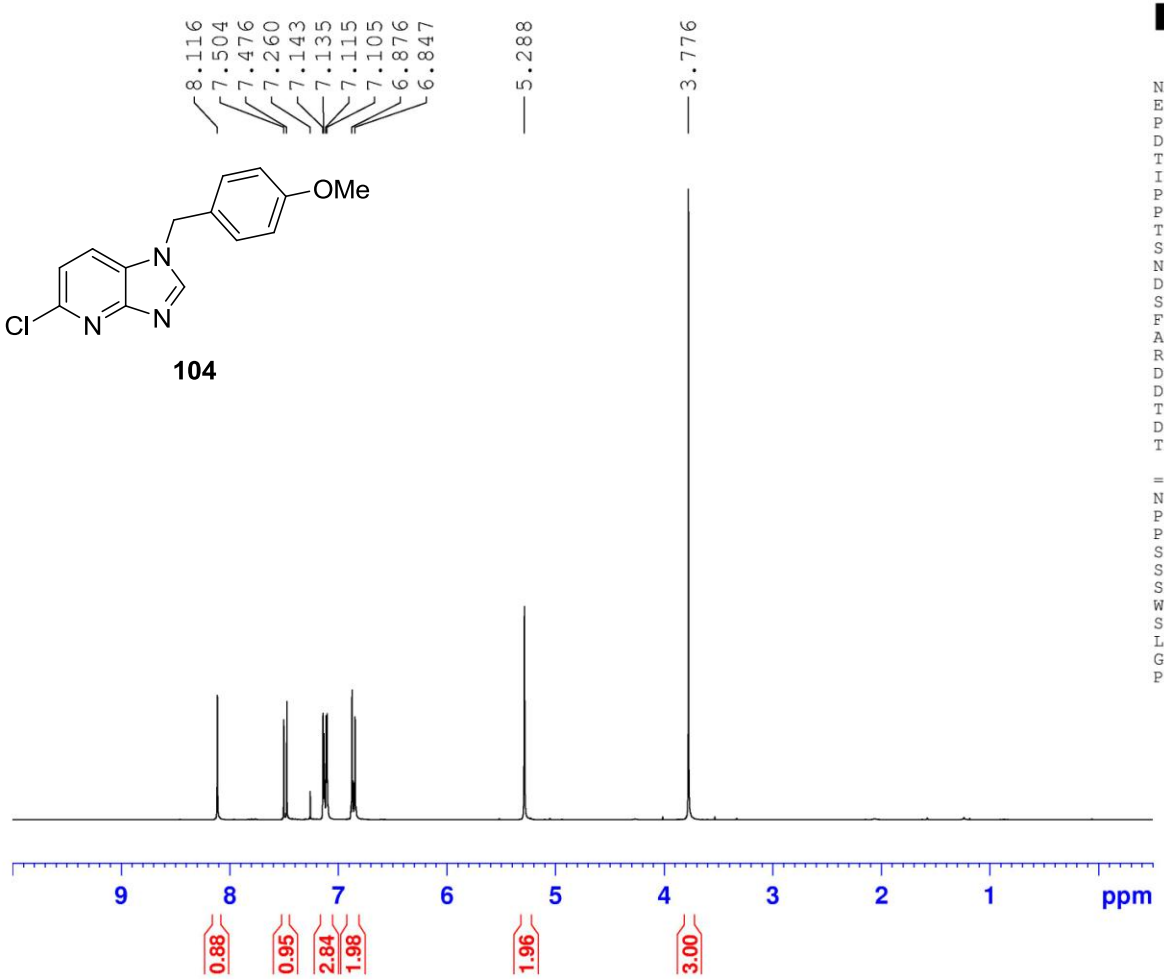
159.911
154.918
146.140
143.994
128.820
126.427
126.198
125.978
118.180
114.670
77.591
77.167
76.743
55.378
49.264



103



AJR-5-282
Post Column

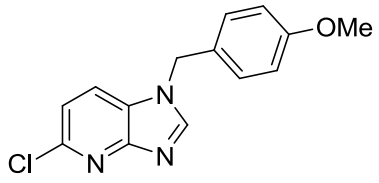


104

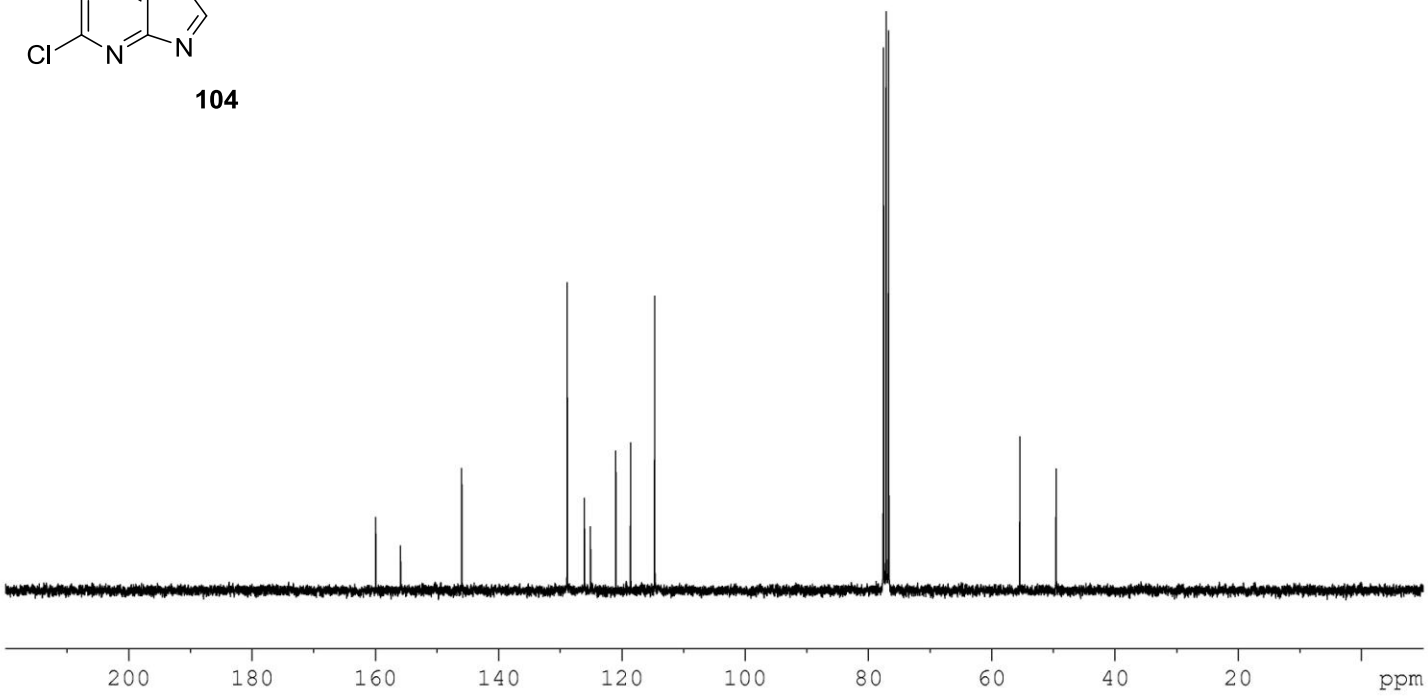
NAME	AJR-5-282
EXPNO	2
PROCNO	1
Date_	20130125
Time	12.56
INSTRUM	spect
PROBHD	5 mm QNP 1H/1
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	0
SWH	3591.954 Hz
FIDRES	0.109618 Hz
AQ	4.5613556 sec
RG	181
DW	139.200 usec
DE	54.00 usec
TE	297.2 K
D1	5.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.75 usec
PL1	0.00 dB
SFO1	300.1315007 MHz
SI	32768
SF	300.1300060 MHz
WDW	EM
SSB	0
LB	0.20 Hz
GB	0
PC	1.00

AJR-5-282
Post Column

159.970
155.962
146.027
145.991
128.911
126.118
125.141
121.013
118.599
114.699
77.587
77.163
76.739
55.445
49.571



104



10.0 VITAE

Adam J. Rosenberg

EDUCATION

January 2010 – September 2013 Syracuse University Syracuse, NY
PhD. Organic Chemistry

June 2006 – June 2009 University of Pittsburgh Pittsburgh, PA
M.S. Organic Chemistry

August 2002 – May 2006 University of Rochester Rochester, NY
B.S. Chemistry B.A. Political Science

RESEARCH EXPERIENCE

January 2010 – September 2013 Syracuse University
Graduate Researcher Syracuse, NY
Advisor: Dr. Daniel Clark

September 2009 – December 2009 LighTouch Medical Inc.
Research Scientist Syracuse, NY
Supervisor: Dr. Joseph Chaiken

June 2006- June 2009 University of Pittsburgh
Graduate Researcher Pittsburgh, PA
Advisor: Dr. Kay Brummond

May 2005- August 2005 Theravance Inc.
Research Internship South San Francisco, CA
Supervisor: Dr. YongQi Mu

June 2004- April 2006 University of Rochester
Undergraduate Researcher Rochester, NY
Advisor: Dr. Robert K. Boeckman Jr.

RESEARCH & LEADERSHIP SKILLS

- Extensive experience in preparing and derivatizing heterocycles.
- Experienced in keeping laboratory notebooks and in good laboratory practices.
- Supervised and trained multiple undergraduate researchers.
- Experienced with milligram to 100 gram multi-step organic lab synthesis.
- Excellent in handling of air and moisture sensitive reactions, utilizing Schlenk techniques as well as glove box experience.
- Experienced in high-throughput parallel reaction and purification techniques.
- Analytical techniques: MS, TLC, LC/MS, GC/MS, NMR, IR, Elemental Analysis.
- Purification techniques: TLC, HPLC, flash chromatography, distillation, recrystallization.
- Experienced in maintaining laboratory instrumentation including: GC, Glove Box and Solvent purification systems.
- Literature searching using Scifinder Scholar, Reaxys, and Web of Science.
- Computer skills, including: Chemdraw, CaCHE, Spartan, Microsoft Office
- Trained in chemical safety procedures

PUBLISHED WORKS

6. **Rosenberg, A.J.;** Wilson, R.; Ahmed, I.; Kaminsky, L.; Clark, D.A. "Palladium catalyzed synthesis of imidazo[4,5-*c*]pyridines" *Manuscript in Preparation*

5. **Rosenberg, A. J.**; Williams, T.M.; Ahmed, I.; Brenner, T.; Clark, D. A. "An Improved Synthesis of Imidazo[4,5-*b*]pyridines & Imidazo[4,5-*b*]pyrazines by mild Palladium catalysis" *Manuscript in Preparation*

4. **Rosenberg, A. J.**; Williams, T. M.; Jordan, A.; Clark, D.A. "Synthesis of

2-amino- imidazo[4,5-*b*]pyridines" *Org. Biomol. Chem.* 2013, 11 (18), 3064-3072

3. **Rosenberg, A. J.**; Clark, D. A. "Total Synthesis of Pentosidine" *Org. Lett.*, **2012**, 14 (17), 4678–4681.

2. **Rosenberg, A. J.**; Zhao, J.; Clark, D. A. "Synthesis of Imidazo[4,5-*b*]pyridines and Imidazo[4,5-*b*]pyrazines by Palladium Catalyzed Amidation of 2-Chloro-3-amino- heterocycles" *Org. Lett.* **2012**, 14(7), 1764-1767. (Highlighted in *Synfacts*, **2012**, 8, 722)

1. Checked Organic Syntheses procedure for "Preparation of 4-Spirocyclohexyloxazolidinone by C-H Bond Nitrene Insertion" by: Kim Huard and Hélène Lebel *Organic Syntheses, Vol. 86, p.59 (2009).*

POSTERS AND PRESENTATIONS

2. **Rosenberg, A. J.**; Clark, D. A. "Synthesis of Imidazo[4,5-b]pyridines & Pyrazines by Palladium Catalyzed Amidation of 2-Chloro-3-amino-heterocycles and Their Application to Natural Product Synthesis." Presented at the Northeast Regional Meeting of the ACS, Rochester, NY October 2nd, 2012

1. **Rosenberg, A. J.**; Clark, D. A. "Toward the Synthesis of Pentosidine" Presented at the 28th Annual Graduate Student Symposium at the University at Buffalo, Buffalo, NY, May 17-18, 2010. Poster Presentation